10/070,794

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=> d his

     (FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006
L1          3955 S "AMPK"
L2          5373 S AMP (W) ACTIVATED (3W) KINASE?
L3          6016 S L1 OR L2
L4           155 S (MUSCULAR OR MUSCLE?)(W) L3
L5            66 S HUMAN AND L4
L6            30 DUP REM L5 (36 DUPLICATES REMOVED)
L7       2037417 S GAMMA
L8             6 S GAMMA AND L6
L9            23 S " R41Q" OR "V40I"
L10            0 S L6 AND L9
L11            1 S L3 AND L9
L12          154 S "PRKAG3"
L13           87 S L7 AND L12
L14            0 S L4 AND L13
L15           28 DUP REM L13 (59 DUPLICATES REMOVED)
                 E ANDERSEN L/AU
L16          523 S E3
                 E LOOFT C/AU
L17          138 S E3
                 E KALM E/AU
L18          514 S E3
                 E GELLIN J/AU
L19          456 S E3
                 E CHARDON P/AU
L20          460 S E3
L21         1957 S L15 OR L16 OR L17 OR L18 OR L19 OR L20
L22            0 S L21 AND L4
L23           26 S L3 AND L21
L24           21 DUP REM L23 (5 DUPLICATES REMOVED)
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 NEWS  7  DEC 21   IPC search and display fields enhanced in CA/CAplus with the
                   IPC reform
 NEWS  8  DEC 23   New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                   USPAT2
 NEWS  9  JAN 13   IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13   New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                   INPADOC
 NEWS 11  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17   IPC 8 in the WPI family of databases including WPIFV
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 NEWS 14  JAN 31   Monthly current-awareness alert (SDI) frequency
                   added to TULSA

 NEWS EXPRESS  JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
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FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006

=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21
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FILE 'MEDLINE' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'EMBASE' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'BIOSIS' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'BIOTECHDS' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'SCISEARCH' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'HCAPLUS' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'NTIS' ENTERED AT 13:57:53 ON 14 FEB 2006

FILE 'LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006


```
=> s "AMPK"
L1         3955 "AMPK"

=> s amp (w) activated (3w) kinase?
L2         5373 AMP (W) ACTIVATED (3W) KINASE?

=> s l1 or l2
L3         6016 L1 OR L2

=> s (muscular or muscle?)(w) l3
L4          155 (MUSCULAR OR MUSCLE?)(W) L3

=> s human and l4
L5           66 HUMAN AND L4

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6           30 DUP REM L5 (36 DUPLICATES REMOVED)

=> d 1-30 ibib ab

L6   ANSWER 1 OF 30     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2005387582     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 16046303
TITLE:              Skeletal muscle AMP-activated
                    protein kinase phosphorylation parallels
                    metabolic phenotype in leptin transgenic mice under dietary
                    modification.
AUTHOR:             Tanaka Tomohiro; Hidaka Shuji; Masuzaki Hiroaki; Yasue
                    Shintaro; Minokoshi Yasuhiko; Ebihara Ken; Chusho Hideki;
                    Ogawa Yoshihiro; Toyoda Taro; Sato Kenji; Miyanaga Fumiko;
                    Fujimoto Muneya; Tomita Tsutomu; Kusakabe Toru; Kobayashi
                    Nozomi; Tanioka Hideki; Hayashi Tatsuya; Hosoda Kiminori;
                    Yoshimatsu Hironobu; Sakata Toshiie; Nakao Kazuwa
CORPORATE SOURCE:   Department of Medicine and Clinical Science, Kyoto
```

University Graduate School of Medicine, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan.
SOURCE: Diabetes, (2005 Aug) 54 (8) 2365-74. Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200510
ENTRY DATE: Entered STN: 20050728
Last Updated on STN: 20051021
Entered Medline: 20051020

AB Leptin augments glucose and lipid metabolism independent of its effect on satiety. Administration of leptin in rodents increases skeletal muscle beta-oxidation by activating AMP-activated protein kinase (AMPK). We previously reported that, as hyperleptinemic as obese **human** subjects, transgenic skinny mice overexpressing leptin in liver (LepTg) exhibit enhanced insulin sensitivity and lipid clearance. To assess skeletal **muscle AMPK** activity in leptin-sensitive and -insensitive states, we examined phosphorylation of AMPK and its target, acetyl CoA carboxylase (ACC), in muscles from LepTg under dietary modification. Here we show that phosphorylation of AMPK and ACC are chronically augmented in LepTg soleus muscle, with a concomitant increase in the AMP-to-ATP ratio and a significant decrease in tissue triglyceride content. Despite preexisting hyperleptinemia, high-fat diet (HFD)-fed LepTg develop obesity, insulin-resistance, and hyperlipidemia. In parallel, elevated soleus AMPK and ACC phosphorylation in regular diet-fed LepTg is attenuated, and tissue triglyceride content is increased in those given HFD. Of note, substitution of HFD with regular diet causes a robust recovery of soleus AMPK and ACC phosphorylation in LepTg, with a higher rate of body weight reduction and a regain of insulin sensitivity. In conclusion, soleus AMPK and ACC phosphorylation in LepTg changes in parallel with its insulin sensitivity under dietary modification, suggesting a close association between skeletal **muscle AMPK** activity and sensitivity to leptin.

L6 ANSWER 2 OF 30 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005140144 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15516364
TITLE: AMP kinase expression and activity in **human** skeletal muscle: effects of immobilization, retraining, and creatine supplementation.
AUTHOR: Eijnde Bert O; Derave Wim; Wojtaszewski Jorgen F P; Richter Erik A; Hespel Peter
CORPORATE SOURCE: Exercise Physiology and Biomechanics Laboratory, Faculty of Kinesiology and Rehabilitation Sciences, Tervuursevest 101, B-3001 Leuven, Belgium.. Bert.OpTEijnde@faber.kuleuven.be
SOURCE: Journal of applied physiology (Bethesda, Md. : 1985), (2005 Apr) 98 (4) 1228-33. Electronic Publication: 2004-10-29. Journal code: 8502536. ISSN: 8750-7587.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200507
ENTRY DATE: Entered STN: 20050318
Last Updated on STN: 20050706
Entered Medline: 20050705

AB The effects of leg immobilization and retraining in combination with oral creatine intake on **muscle AMP-activated** protein **kinase** (AMPK) protein expression and phosphorylation status were investigated. A double-blind trial was performed in young

healthy volunteers (n = 22). A cast immobilized the right leg for 2 wk, whereafter the knee-extensor muscles of that leg were retrained for 6 wk. Half of the subjects received creatine monohydrate throughout the study (Cr; from 15 g down to 2.5 g daily), and the others ingested placebo (P; maltodextrin). Before and after immobilization and retraining, needle biopsies were taken from the right and left vastus lateralis muscles. In the right leg of P and Cr, immobilization did not affect AMPK alpha1-, alpha2-, and beta2-subunit expression or AMPK alpha-subunit phosphorylation status. However, irrespective of the treatment received, retraining increased the degree of alpha-subunit phosphorylation by approximately 25% (P <0.05) and increased AMPK alpha1-subunit expression (P <0.05) in both groups. From the start to the end of the study, AMPK subunit protein expression and alpha-subunit phosphorylation status were unchanged in the contralateral control leg. It is concluded that immobilization-induced muscle inactivity for 2 wk does not alter AMPK alpha1-, alpha2-, and beta2-subunit expression or alpha-AMPK phosphorylation status. Furthermore, the present observations indicate that AMPK probably is not implicated in the previously reported beneficial effects of oral creatine supplementation on muscle during immobilization and rehabilitative weight training.

L6 ANSWER 3 OF 30 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005551226 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16051629
TITLE: Short-term exercise training in **humans** reduces AMPK signalling during prolonged exercise independent of muscle glycogen.
COMMENT: Comment in: J Physiol. 2005 Oct 15;568(Pt 2):355. PubMed ID: 16081480
AUTHOR: McConell Glenn K; Lee-Young Robert S; Chen Zhi-Ping; Stepto Nigel K; Huynh Ngan N; Stephens Terry J; Canny Benedict J; Kemp Bruce E
CORPORATE SOURCE: Department of Physiology, University of Melbourne, Parkville, Victoria, Australia.. mcconell@unimelb.edu.au
SOURCE: The Journal of physiology, (2005 Oct 15) 568 (Pt 2) 665-76. Electronic Publication: 2005-07-28. Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 20051018 Last Updated on STN: 20051228 Entered Medline: 20051227

AB We examined the effect of short-term exercise training on skeletal **muscle AMP-activated** protein **kinase** (AMPK) signalling and muscle metabolism during prolonged exercise in **humans**. Eight sedentary males completed 120 min of cycling at 66 +/- 1% , then exercise trained for 10 days, before repeating the exercise bout at the same absolute workload. Participants rested for 72 h before each trial while ingesting a high carbohydrate diet (HCHO). Exercise training significantly (P < 0.05) attenuated exercise-induced increases in skeletal muscle free AMP: ATP ratio and glucose disposal and increased fat oxidation. Exercise training abolished the 9-fold increase in AMPK alpha2 activity observed during pretraining exercise. Since training increased muscle glycogen content by 93 +/- 12% (P < 0.01), we conducted a second experiment in seven sedentary male participants where muscle glycogen content was essentially matched pre- and post-training by exercise and a low CHO diet (LCHO; post-training muscle glycogen 52 +/- 7% less than in HCHO, P < 0.001). Despite the difference in muscle glycogen levels in the two studies we obtained very similar results. In both studies the increase in ACCbeta Ser(221) phosphorylation was reduced during exercise

after training. In conclusion, there is little activation of AMPK signalling during prolonged exercise following short-term exercise training suggesting that other factors are important in the regulation of glucose disposal and fat oxidation under these circumstances. It appears that muscle glycogen is not an important regulator of AMPK activation during exercise in **humans** when exercise is begun with normal or high muscle glycogen levels.

L6 ANSWER 4 OF 30 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2005193832 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15718261
TITLE: 5'AMP activated protein kinase expression in **human** skeletal muscle: effects of strength training and type 2 diabetes.
AUTHOR: Wojtaszewski Jorgen F P; Birk Jesper B; Frosig Christian; Holten Mads; Pilegaard Henriette; Dela Flemming
CORPORATE SOURCE: The Institute of Exercise and Sport Sciences, The Copenhagen Muscle Research Centre, University of Copenhagen, 13 Universitetsparken, 2100-Copenhagen, Denmark.. jwojtaszewski@aki.ku.dk
SOURCE: Journal of physiology, (2005 Apr 15) 564 (Pt 2) 563-73. Electronic Publication: 2005-02-17. Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 20050414
Last Updated on STN: 20050824
Entered Medline: 20050823

AB Strength training enhances insulin sensitivity and represents an alternative to endurance training for patients with type 2 diabetes (T2DM). The 5'AMP-activated protein kinase (AMPK) may mediate adaptations in skeletal muscle in response to exercise training; however, little is known about adaptations within the AMPK system itself. We investigated the effect of strength training and T2DM on the isoform expression and the heterotrimeric composition of the AMPK in **human** skeletal muscle. Ten patients with T2DM and seven healthy subjects strength trained (T) one leg for 6 weeks, while the other leg remained untrained (UT). Muscle biopsies were obtained before and after the training period. Basal AMPK activity and protein/mRNA expression of both catalytic (alpha1 and alpha2) and regulatory (beta1, beta2, gamma1, gamma2a, gamma2b and gamma3) AMPK isoforms were independent of T2DM, whereas the protein content of alpha1 (+16%), beta2 (+14%) and gamma1 (+29%) was higher and the gamma3 content was lower (-48%) in trained compared with untrained muscle (all $P < 0.01$). The majority of alpha protein co-immunoprecipitated with beta2 and alpha2/beta2 accounted for the majority of these complexes. gamma3 was only associated with alpha2 and beta2 subunits, and accounted for approximately 20% of all alpha2/beta2 complexes. The remaining alpha2/beta2 and the alpha1/beta2 complexes were associated with gamma1. The trimer composition was unaffected by T2DM, whereas training induced a shift from gamma3- to gamma1-containing trimers. The data question **muscular AMPK** as a primary cause of T2DM whereas the maintained function in patients with T2DM makes **muscular AMPK** an obvious therapeutic target. In **human** skeletal muscle only three of 12 possible AMPK trimer combinations exist, and the expression of the subunit isoforms is susceptible to moderate strength training, which may influence metabolism and improve energy homeostasis in trained muscle.

L6 ANSWER 5 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:519270 BIOSIS
DOCUMENT NUMBER: PREV200510297184

TITLE: Effects of PPAR-alpha and PPAR-gamma agonists on **muscle AMPK** activity and insulin resistance in patients with type 2 diabetes mellitus.
AUTHOR(S): Bajaj, M. [Reprint Author]; Suraamornkul, S.; Sriwijilkamol, A.; Musi, N.; DeFronzo, R.
CORPORATE SOURCE: Univ Texas, Hlth Sci Ctr, Dept Med, Diabet Div, San Antonio, TX USA
SOURCE: Diabetologia, (2005) Vol. 48, No. Suppl. 1, pp. A280. Meeting Info.: 41st Annual Meeting of the European-Association-for-the-Study-of-Diabetes. Athens, GREECE. September 10 -15, 2005. European Assoc Study Diabet.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Nov 2005
Last Updated on STN: 23 Nov 2005

L6 ANSWER 6 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:14452 BIOSIS
DOCUMENT NUMBER: PREV200600017485
TITLE: Effects of PPAR-alpha and PPAR-gamma agonists on **muscle AMPK** activity in patients with type 2 diabetes (T2DM).
AUTHOR(S): Bajaj, Mandeep [Reprint Author]; Suraamornkul, Swangjit; Sriwijilkamol, Apiradee; Musi, Nicolas; Defronzo, Ralph
SOURCE: Diabetes, (2005) Vol. 54, No. Suppl. 1, pp. A151. Meeting Info.: 65th Annual Meeting of the American-Diabetes-Association. San Diego, CA, USA. June 10 -14, 2005. Amer Diabet Assoc.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Dec 2005
Last Updated on STN: 21 Dec 2005

L6 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:550994 HCAPLUS
DOCUMENT NUMBER: 141:101183
TITLE: **Human** cDNA sequences, their encoded polypeptides, and diagnostic and therapeutic uses for obesity and diabetes
INVENTOR(S): Berghs, Constance; Catterton, Elina; Ellerman, Karen; Ort, Tatiana; Rieger, Daniel; Chaudhuri, Amitabha
PATENT ASSIGNEE(S): Curagen Corporation, USA
SOURCE: PCT Int. Appl., 571 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004056961	A2	20040708	WO 2003-US34114	20031027
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2002-421239P	P	20021025
US 2002-421700P	P	20021028
US 2002-422776P	P	20021031
US 2002-426197P	P	20021113
US 2002-435498P	P	20021220
US 2002-435510P	P	20021220
US 2002-435568P	P	20021220
US 2003-456812P	P	20030321

AB The invention claims 47 NOVX (where X=1-47) target polypeptide sequences and their corresponding nucleic acids as well as their variants. These NOVX polypeptides have homol. to known protein families, including long-chain fatty acid CoA ligase 2, membrane copper amine oxidase, protein kinases, and AMP deaminase. The invention further claims methods of identifying compds. that modulate target polypeptide activity, where a test compound is combined with a target polypeptide and a substrate of the target polypeptide and where a determination is made as to whether the test compound
modulates activity of the target polypeptide. The test compds. could be small mol. drugs used for treatment of obesity, diabetes, insulin resistance, and for enhancement of insulin secretion.

L6 ANSWER 8 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:148015 HCAPLUS
DOCUMENT NUMBER: 140:369047
TITLE: Postcontraction insulin sensitivity: relationship with contraction protocol, glycogen concentration, and 5' AMP-activated protein kinase phosphorylation
AUTHOR(S): Kim, Junghoon; Solis, Raquel S.; Arias, Edward B.; Cartee, Gregory D.
CORPORATE SOURCE: Department of Kinesiology and Biodynamics Laboratory, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of Applied Physiology (2004), 96(2), 575-583
CODEN: JAPHEV; ISSN: 8750-7587
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exercise enhances insulin-stimulated glucose transport (GT) in skeletal muscle. Evidence suggests that 5'-AMP-activated protein kinase (AMPK) and glycogen may be important for enhanced insulin sensitivity. The authors' goals were to investigate the effect of various in situ muscle contraction protocols on insulin-stimulated GT and assess the relationship of contraction-induced changes in AMPK and glycogen with postcontraction improvement in insulin-stimulated GT. Rats were anesthetized, both ulnar nerves were exposed, and one nerve was elec. stimulated to contract forelimb muscles. The authors performed a series of five expts., sequentially varying only one contraction parameter (train duration, train rate, pulse frequency, number of 5-min bouts, or pulse duration) while holding the others constant Both epitrochlearis muscles were dissected out and incubated for 3.5 h before measurement of GT. For each contraction parameter studied, the authors identified an apparent threshold value that did not induce a significant increase in insulin-stimulated GT and an apparent peak value, above which there was a plateau or decline in insulin-stimulated GT. Using other rats, the authors evaluated **muscle AMPK** phosphorylation and glycogen concentration immediately postcontraction. AMPK phosphorylation and reduction in glycogen were increased compared with resting controls in each protocol, which had previously been shown to increase insulin-stimulated GT, as well as in several protocols that did not significantly increase insulin-stimulated GT. These data suggest that contraction-induced AMPK phosphorylation and decrease in glycogen may be necessary but are not sufficient for the postcontraction increase in insulin-stimulated GT in rat skeletal muscle.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:976685 HCAPLUS
DOCUMENT NUMBER: 141:392568
TITLE: Regulation of hormone-sensitive lipase activity and Ser563 and Ser565 phosphorylation in **human** skeletal muscle during exercise
AUTHOR(S): Roepstorff, Carsten; Vistisen, Bodil; Donsmark, Morten; Nielsen, Jakob N.; Galbo, Henrik; Green, Kevin A.; Hardie, D. Grahame; Wojtaszewski, Jorgen F. P.; Richter, Erik A.; Kiens, Bente
CORPORATE SOURCE: The Copenhagen Muscle Research Centre, Department of Human Physiology, Institute of Exercise and Sport Sciences, University of Copenhagen, Copenhagen, DK-2100, Den.
SOURCE: Journal of Physiology (Oxford, United Kingdom) (2004), 560(2), 551-562
CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hormone-sensitive lipase (HSL) catalyzes the hydrolysis of myocellular triacylglycerol (MCTG), which is a potential energy source during exercise. Therefore, it is important to elucidate the regulation of HSL activity in **human** skeletal muscle during exercise. The main purpose of the present study was to investigate the role of 5'AMP-activated protein kinase (AMPK) in the regulation of muscle HSL activity and Ser565 phosphorylation (the presumed AMPK target site) in healthy, moderately trained men during 60 min bicycling (65% Vo2peak). α2AMPK activity during exercise was manipulated by studying subjects with either low (LG) or high (HG) muscle glycogen content. HSL activity was distinguished from the activity of other neutral lipases by immunoinhibition of HSL using an anti-HSL antibody. During exercise a 62% higher ($P < 0.01$) α2AMPK activity in LG than in HG was paralleled by a similar difference (61%, $P < 0.01$) in HSL Ser565 phosphorylation but without any difference between trials in HSL activity or MCTG hydrolysis. HSL activity was increased (117%, $P < 0.05$) at 30 min of exercise but not at 60 min of exercise. In both trials, HSL phosphorylation on Ser563 (a presumed PKA target site) was not increased by exercise despite a fourfold increase ($P < 0.001$) in plasma adrenaline. ERK1/2 phosphorylation was increased by exercise in both trials ($P < 0.001$) and was higher in LG than in HG both at rest and during exercise ($P = 0.06$). In conclusion, the present study suggests that AMPK phosphorylates HSL on Ser565 in **human** skeletal muscle during exercise with reduced muscle glycogen. Apparently, HSL Ser565 phosphorylation by AMPK during exercise had no effect on HSL activity. Alternatively, other factors including ERK may have counterbalanced any effect of AMPK on HSL activity.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:152837 HCAPLUS
DOCUMENT NUMBER: 140:197419
TITLE: AMPK activity and isoform protein expression are similar in muscle of obese subjects with and without type 2 diabetes
AUTHOR(S): Hojlund, Kurt; Mustard, Kirsty J.; Staehr, Peter; Hardie, D. Grahame; Beck-Nielsen, Henning; Richter, Erik A.; Wojtaszewski, Jorgen F. P.
CORPORATE SOURCE: Diabetes Research Centre, Odense University Hospital, University of Southern Denmark and Department of Endocrinology, Odense, DK-5000, Den.

SOURCE: American Journal of Physiology (2004), 286(2, Pt. 1), E239-E244
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acute or chronic activation of AMP-activated protein kinase (AMPK) increases insulin sensitivity. Conversely, reduced expression and/or function of AMPK might play a role in insulin resistance in type 2 diabetes. Thus protein expression of the seven subunit isoforms of AMPK and activities and/or phosphorylation of AMPK and acetyl-CoA carboxylase-β (ACCβ) was measured in skeletal muscle from obese type 2 diabetic and well-matched control subjects during euglycemic-hyperinsulinemic clamps. Protein expression of all AMPK subunit isoforms (α1, α2, β1, β2, γ1, γ2, and γ3) in muscle of obese type 2 diabetic subjects was similar to that of control subjects. In addition, α1- and α2-associated activities of AMPK, phosphorylation of α-AMPK subunits at Thr172, and phosphorylation of ACCβ at Ser221 showed no difference between the two groups and were not regulated by physiol. concns. of insulin. These data suggest that impaired insulin action on glycogen synthesis and lipid oxidation in skeletal muscle of obese type 2 diabetic subjects is unlikely to involve changes in AMPK expression and activity.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 30 EMBASE

ACCESSION NUMBER: 2004054106 EMBASE
TITLE: Cloning and characterization of mouse 5'-AMP-activated protein kinase γ3 subunit.
AUTHOR: Yu H.; Fujii N.; Hirshman M.F.; Pomerleau J.M.; Goodyear L.J.
CORPORATE SOURCE: L.J. Goodyear, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, United States.
laurie.goodyear@joslin.harvard.edu
SOURCE: American Journal of Physiology - Cell Physiology, (2004) Vol. 286, No. 2 55-2, pp. C283-C292. .
Refs: 51
ISSN: 0363-6143 CODEN: AJPCDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040220
Last Updated on STN: 20040220

AB Naturally occurring mutations in the regulatory γ-subunit of 5'-AMP-activated protein kinase (AMPK) can result in pronounced pathological changes that may stem from increases in muscle glycogen levels, making it critical to understand the role(s) of the γ-subunit in AMPK function. In this study we cloned the mouse AMPKγ3 subunit and revealed that there are two transcription start sites, which result in a long form, γ3L (AF525500) and a short form, γ3S (AF525501). AMPKγ3L is the predominant form in mouse and is specifically expressed in mouse skeletal muscle at the protein level. In skeletal muscle, AMPKγ3 shows higher levels of expression in fast-twitch white glycolytic muscle (type IIb) compared with fast-twitch red oxidative glycolytic muscle (type IIa), whereas γ3 is undetectable in soleus muscle, a slow-twitch oxidative muscle with predominantly type I fibers. AMPK-γ3 can coimmunoprecipititate with both α and β AMPK subunits. Overexpression of γ3S

and γ3L in mouse tibialis anterior muscle in vivo has no effect on α1 and α2 subunit expression and does not alter AMPKα2 catalytic activity. However, γ3S and γ3L overexpression significantly increases AMPKα1 phosphorylation and activity by .apprx.50%. The increase in AMPKα1 activity is not associated with alterations in glycogen accumulation or glycogen synthase expression. In conclusion, the γ3 subunit of AMPK is highly expressed in fast-twitch glycolytic skeletal muscle, and wild-type γ3 functions in the regulation of α1 catalytic activity, but it is not associated with changes in muscle glycogen concentrations.

L6 ANSWER 12 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:292272 BIOSIS
DOCUMENT NUMBER: PREV200400291754
TITLE: Weight Loss and Resistive Training Decreases Skeletal **Muscle AMPK**(alpha)1 in Obese Women.
AUTHOR(S): Ryan, Alice [Reprint Author]; Gray, Melissa; Joseph, Lyndon; McLenithan, John
CORPORATE SOURCE: GRECC, VA Medical Center, 10 North Greene St, Baltimore, MD, 21201, USA
aryan@grecc.umaryland.edu
SOURCE: FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 851.29. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jun 2004
Last Updated on STN: 23 Jun 2004

AB AMP-activated protein kinase (AMPK), which is activated during muscle contraction, impacts acute exercise stimulated glucose transport as well as fat oxidation. The purpose of this study was to determine the effects of weight loss combined with resistive training (WL+RT) on AMP kinase (AMPK(alpha) 1, AMPK(alpha)2), GLUT4 and fat oxidation in postmenopausal women. Seven sedentary, obese (BMI = 30 +/- 1 kg/m2, X +/- SEM) women (56 +/- 2 yrs) completed 6 mos (3x/wk) WL+RT. Total body fat mass was determined by DXA and muscular strength by a 3-repetition maximum test. Vastus lateralis muscle biopsies were conducted in order to measure skeletal **muscle AMPK**(alpha)1 and AMPK(alpha)2 protein levels and GLUT4 by western blotting. Glucose utilization (M) was measured during the last 60 min of 3-hr hyperinsulinemic-euglycemic clamps (40 mU m2 min-1). Body weight, total fat mass, and %fat decreased after WL+RT ($P < 0.01$). Upper and lower body strength increased by 23 and 27% ($P<0.01$). M increased by 11% ($P < 0.05$) and fat oxidation decreased ($P < 0.05$). Skeletal **muscle AMPK**(alpha)1 decreased 118% ($P = 0.02$) whereas AMPK(alpha)2 and GLUT4 protein levels did not change with WL+RT. Thus, 6 months of WL+RT results in significant increases in glucose utilization and decreases in fat oxidation and AMPkinase(alpha)1 levels in obese postmenopausal women. Support: NIH Grants K01-AG00747, R29-A614066, and Department of Veterans Affairs .

L6 ANSWER 13 OF 30 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2003432854 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12941758
TITLE: Effect of exercise intensity on skeletal **muscle AMPK** signaling in **humans**.
AUTHOR: Chen Zhi-Ping; Stephens Terry J; Murthy Sid; Canny Benedict J; Hargreaves Mark; Witters Lee A; Kemp Bruce E; McConell Glenn K
CORPORATE SOURCE: St. Vincent's Institute of Medical Research, University of

Melbourne, Fitzroy, Victoria, Australia.
CONTRACT NUMBER: DK35712 (NIDDK)
SOURCE: Diabetes, (2003 Sep) 52 (9) 2205-12.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030917
Last Updated on STN: 20031008
Entered Medline: 20031007

AB The effect of exercise intensity on skeletal **muscle AMP -activated** protein **kinase** (AMPK) signaling and substrate metabolism was examined in eight men cycling for 20 min at each of three sequential intensities: low (40 +/- 2% VO(2) peak), medium (59 +/- 1% VO(2) peak), and high (79 +/- 1% VO(2) peak). Muscle free AMP/ATP ratio only increased at the two higher exercise intensities ($P < 0.05$). AMPK alpha 1 (1.5-fold) and AMPK alpha 2 (5-fold) activities increased from low to medium intensity, with AMPK alpha 2 activity increasing further from medium to high intensity. The upstream AMPK kinase activity was substantial at rest and only increased 50% with exercise, indicating that, initially, signaling through AMPK did not require AMPK kinase posttranslational modification. Acetyl-CoA carboxylase (ACC)-beta phosphorylation was sensitive to exercise, increasing threefold from rest to low intensity, whereas neuronal NO synthase (nNOS) micro phosphorylation was only observed at the higher exercise intensities. Glucose disappearance (tracer) did not increase from rest to low intensity, but increased sequentially from low to medium to high intensity. Calculated fat oxidation increased from rest to low intensity in parallel with ACC beta phosphorylation, then declined during high intensity. These results indicate that ACC beta phosphorylation is especially sensitive to exercise and tightly coupled to AMPK signaling and that AMPK activation does not depend on AMPK kinase activation during exercise.

L6 ANSWER 14 OF 30 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2003137815 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12488245
TITLE: Regulation of 5'AMP-activated protein kinase activity and substrate utilization in exercising **human** skeletal muscle.
AUTHOR: Wojtaszewski Jorgen F P; MacDonald Christopher; Nielsen Jakob N; Hellsten Ylva; Hardie D Grahame; Kemp Bruce E; Kiens Bente; Richter Erik A
CORPORATE SOURCE: Department of Human Physiology, Institute of Exercise and Sport Sciences, University of Copenhagen, 2100 Copenhagen, Denmark.. Jwojtaszewski@aki.ku.dk
SOURCE: American journal of physiology. Endocrinology and metabolism, (2003 Apr) 284 (4) E813-22. Electronic Publication: 2002-12-17.
Journal code: 100901226. ISSN: 0193-1849.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030326
Last Updated on STN: 20030416
Entered Medline: 20030410

AB The metabolic role of 5'AMP-activated protein kinase (AMPK) in regulation of skeletal muscle metabolism in **humans** is unresolved. We measured isoform-specific AMPK activity and beta-acetyl-CoA carboxylase

(ACCbeta) Ser(221) phosphorylation and substrate balance in skeletal muscle of eight athletes at rest, during cycling exercise for 1 h at 70% peak oxygen consumption, and 1 h into recovery. The experiment was performed twice, once in a glycogen-loaded (glycogen concentration approximately 900 mmol/kg dry wt) and once in a glycogen-depleted (glycogen concentration approximately 160 mmol/kg dry wt) state. At rest, plasma long-chain fatty acids (FA) were twofold higher in the glycogen-depleted than in the loaded state, and muscle alpha1 AMPK (160%) and alpha2 AMPK (145%) activities and ACCbeta Ser(221) phosphorylation (137%) were also significantly higher in the glycogen-depleted state. During exercise, alpha2 AMPK activity, ACCbeta Ser(221) phosphorylation, plasma catecholamines, and leg glucose and net FA uptake were significantly higher in the glycogen-depleted than in the glycogen-loaded state without apparent differences in muscle high-energy phosphates. Thus exercise in the glycogen-depleted state elicits an enhanced uptake of circulating fuels that might be associated with elevated **muscle AMPK** activation. It is concluded that **muscle AMPK** activity and ACCbeta Ser(221) phosphorylation at rest and during exercise are sensitive to the fuel status of the muscle. During exercise, this dependence may in part be mediated by humoral factors.

L6 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:153608 HCAPLUS
DOCUMENT NUMBER: 139:4309
TITLE: 5'-AMP-activated protein kinase activity and subunit expression in exercise-trained **human** skeletal muscle
AUTHOR(S): Nielsen, Jakob N.; Mustard, Kirsty J. W.; Graham, Drew A.; Yu, Haiyan; MacDonald, Christopher S.; Pilegaard, Henriette; Goodyear, Laurie J.; Hardie, D. Grahame; Richter, Erik A.; Wojtaszewski, Jorgen F. P.
CORPORATE SOURCE: Institute of Exercise and Sport Sciences, Copenhagen Muscle Research Centre, University of Copenhagen, Copenhagen, DK-2100, Den.
SOURCE: Journal of Applied Physiology (2003), 94(2), 631-641
CODEN: JAPHEV; ISSN: 8750-7587
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5'-AMP-activated protein kinase (AMPK) has been proposed to be a pivotal factor in cellular responses to both acute exercise and exercise training. To investigate whether protein levels and gene expression of catalytic (α1, α2) and regulatory (β1, β2, γ1, γ2, γ3) AMPK subunits and exercise-induced AMPK activity are influenced by exercise training status, muscle biopsies were obtained from 7 endurance exercise-trained and 7 sedentary young healthy men. The α1- and α2-AMPK mRNA contents in trained subjects were both 117 ± 2% of that in sedentary subjects (not significant), whereas mRNA for γ3 was 61 ± 1% of that in sedentary subjects (not significant). The level of α1-AMPK protein in trained subjects was 185 ± 34% of that in sedentary subjects ($P < 0.05$), whereas the levels of the remaining subunits (α2, β1, β2, γ1, γ2, γ3) were similar in trained and sedentary subjects. At the end of 20 min of cycle exercise at 80% of peak O2 uptake, the increase in phosphorylation of α-AMPK (Thr-172) was blunted in the trained group (138 ± 38% above rest) compared with the sedentary group (353 ± 63% above rest) ($P < 0.05$). Acetyl CoA-carboxylase β-phosphorylation (Ser-221), which is a marker for in vivo AMPK activity, was increased by exercise in both groups but to a lower level in trained subjects (32 ± 5 arbitrary units) than in sedentary controls (45 ± 1 arbitrary units) ($P < 0.01$). In conclusion, trained **human** skeletal muscle has increased α1-AMPK protein levels and blunted AMPK activation during exercise.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 30 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:686093 SCISEARCH
THE GENUINE ARTICLE: 708CK
TITLE: Physiological role of AMP-activated protein kinase in the heart: graded activation during exercise
AUTHOR: Coven D L; Hu X Y; Cong L; Bergeron R; Shulman G I; Hardie D G; Young L H (Reprint)
CORPORATE SOURCE: Yale Univ, Sch Med, Sect Cardiovasc Med, Dept Internal Med, 323 FMP, 333 Cedar St, New Haven, CT 06520 USA (Reprint); Yale Univ, Sch Med, Sect Cardiovasc Med, Dept Internal Med, New Haven, CT 06520 USA; Yale Univ, Sch Med, Endocrinol Sect, Dept Internal Med, New Haven, CT 06520 USA; Yale Univ, Sch Med, Metab Sect, Dept Internal Med, New Haven, CT 06520 USA; Yale Univ, Sch Med, Howard Hughes Med Inst, New Haven, CT 06510 USA; Univ Dundee, Fac Life Sci, Div Mol Physiol, Dundee DD1 5EH, Scotland
COUNTRY OF AUTHOR: USA; Scotland
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-ENDOCRINOLOGY AND METABOLISM, (SEP 2003) Vol. 285, No. 3, pp. E629-E636. ISSN: 0193-1849.
PUBLISHER: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 61
ENTRY DATE: Entered STN: 29 Aug 2003
Last Updated on STN: 29 Aug 2003

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB AMP-activated protein kinase (AMPK) is emerging as a key signaling pathway that modulates cellular metabolic processes. In skeletal **muscle**, **AMPK** is activated during exercise. Increased myocardial substrate metabolism during exercise could be explained by AMPK activation. Although AMPK is known to be activated during myocardial ischemia, it remains uncertain whether AMPK is activated in response to the physiological increases in cardiac work associated with exercise. Therefore, we evaluated cardiac AMPK activity in rats at rest and after 10 min of treadmill running at moderate (15% grade, 16 m/min) or high (15% grade, 32 m/min) intensity. Total AMPK activity in the heart increased in proportion to exercise intensity ($P < 0.05$). AMPK activity associated with the α(2)-catalytic subunit increased 2.8 +/- 0.4-fold ($P < 0.02$ vs. rest) and 4.5 +/- 0.6-fold ($P < 0.001$ vs. rest) with moderate- and high-intensity exercise, respectively. AMPK activity associated with the α(1)-subunit increased to a lesser extent. Phosphorylation of the Thr(172)-regulatory site on AMPK α-catalytic subunits increased during exercise ($P < 0.001$). There was no increase in Akt phosphorylation during exercise. The changes in AMPK activity during exercise were associated with physiological AMPK effects (GLUT4 translocation to the sarcolemma and ACC phosphorylation). Thus cardiac AMPK activity increases progressively with exercise intensity, supporting the hypothesis that AMPK has a physiological role in the heart.

L6 ANSWER 17 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003116970 EMBASE
TITLE: Regulation of 5'-AMP-activated protein kinase activity and substrate utilization in exercising **human** skeletal muscle.
AUTHOR: Wojtaszewski J.F.P.; MacDonald C.; Nielsen J.N.; Hellsten Y.; Grahame Hardie D.; Kemp B.E.; Kiens B.; Richter E.A.
CORPORATE SOURCE: J.F.P. Wojtaszewski, Copenhagen Muscle Research Centre, Inst. of Exercise and Sport Sciences, Univ. of Copenhagen,

13 Universitetsparken, 2100 Copenhagen, Denmark. Jwojtaszewski@aki.ku.dk
SOURCE: American Journal of Physiology - Endocrinology and Metabolism, (1 Apr 2003) Vol. 284, No. 4 47-4, pp. E813-E822. .
Refs: 61
ISSN: 0193-1849 CODEN: AJPMD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030403
Last Updated on STN: 20030403

AB The metabolic role of 5'AMP-activated protein kinase (AMPK) in regulation of skeletal muscle metabolism in **humans** is unresolved. We measured isoform-specific AMPK activity and β-acetyl-CoA carboxylase (ACCβ) Ser(221) phosphorylation and substrate balance in skeletal muscle of eight athletes at rest, during cycling exercise for 1 h at 70% peak oxygen consumption, and 1 h into recovery. The experiment was performed twice, once in a glycogen-loaded (glycogen concentration .apprx.900 mmol/kg dry wt) and once in a glycogen-depleted (glycogen concentration .apprx.160 mmol/kg dry wt) state. At rest, plasma long-chain fatty acids (FA) were two-fold higher in the glycogen-depleted than in the loaded state, and muscle α1 AMPK (160%) and α2 AMPK (145%) activities and ACCP Ser(221) phosphorylation (137%) were also significantly higher in the glycogen-depleted state. During exercise, α2 AMPK activity, ACCβ Ser(221) phosphorylation, plasma catecholamines, and leg glucose and net FA uptake were significantly higher in the glycogen-depleted than in the glycogen-loaded state without apparent differences in muscle high-energy phosphates. Thus exercise in the glycogen-depleted state elicits an enhanced uptake of circulating fuels that might be associated with elevated **muscle AMPK** activation. It is concluded that **muscle AMPK** activity and ACCβ Ser(221) phosphorylation at rest and during exercise are sensitive to the fuel status of the muscle. During exercise, this dependence may in part be mediated by humoral factors.

L6 ANSWER 18 OF 30 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002140559 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11832374
TITLE: Progressive increase in **human** skeletal muscle AMPKalpha2 activity and ACC phosphorylation during exercise.
AUTHOR: Stephens T J; Chen Z-P; Canny B J; Michell B J; Kemp B E; McConell G K
CORPORATE SOURCE: Department of Physiology, Monash University, Clayton, Victoria 3800, Australia.
SOURCE: American journal of physiology. Endocrinology and metabolism, (2002 Mar) 282 (3) E688-94.
Journal code: 100901226. ISSN: 0193-1849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020307
Last Updated on STN: 20020320
Entered Medline: 20020319

AB The effect of prolonged moderate-intensity exercise on **human** skeletal **muscle AMP-activated** protein **kinase** (AMPK)alpha1 and -alpha2 activity and acetyl-CoA carboxylase (ACCbeta) and neuronal nitric oxide synthase (nNOSmu)

phosphorylation was investigated. Seven active healthy individuals cycled for 30 min at a workload requiring 62.8 +/- 1.3% of peak O(2) consumption (VO(2 peak)) with muscle biopsies obtained from the vastus lateralis at rest and at 5 and 30 min of exercise. AMPKalpha1 activity was not altered by exercise; however, AMPKalpha2 activity was significantly ($P < 0.05$) elevated after 5 min (approximately 2-fold), and further elevated ($P < 0.05$) after 30 min (approximately 3-fold) of exercise. ACCbeta phosphorylation was increased ($P < 0.05$) after 5 min (approximately 18-fold compared with rest) and increased ($P < 0.05$) further after 30 min of exercise (approximately 36-fold compared with rest). Increases in AMPKalpha2 activity were significantly correlated with both increases in ACCbeta phosphorylation and reductions in muscle glycogen content. Fat oxidation tended ($P = 0.058$) to increase progressively during exercise. Muscle creatine phosphate was lower ($P < 0.05$), and muscle creatine, calculated free AMP, and free AMP-to-ATP ratio were higher ($P < 0.05$) at both 5 and 30 min of exercise compared with those at rest. At 30 min of exercise, the values of these metabolites were not significantly different from those at 5 min of exercise. Phosphorylation of nNOSmu was variable, and despite the mean doubling with exercise, statistically significance was not achieved ($P = 0.304$). Western blots indicated that AMPKapproximately 2 was associated with both nNOSmu and ACCbeta consistent with them both being substrates of AMPKalpha2 in vivo. In conclusion, AMPKalpha2 activity and ACCbeta phosphorylation increase progressively during moderate exercise at approximately 60% of VO(2 peak) in **humans**, with these responses more closely coupled to muscle glycogen content than muscle AMP/ATP ratio.

L6 ANSWER 19 OF 30 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:525507 SCISEARCH
THE GENUINE ARTICLE: 557XP
TITLE: Short-term exercise training suppresses increases in **human** skeletal **muscle AMPK** activity during prolonged exercise
AUTHOR: Mcconell G K (Reprint); Stepto N K; Chen Z P; Stephens T J; Huynh N N; Canny B J; Kemp B E
SOURCE: DIABETES, (JUN 2002) Vol. 51, Supp. [2], pp. A253-A254. MA 1028.
ISSN: 0012-1797.
PUBLISHER: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 12 Jul 2002
Last Updated on STN: 12 Jul 2002

L6 ANSWER 20 OF 30 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 2002324857 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12067859
TITLE: Effects of endurance training on activity and expression of AMP-activated protein kinase isoforms in rat muscles.
AUTHOR: Durante Paula E; Mustard Kirsty J; Park Soo-Hyun; Winder William W; Hardie D Grahame
CORPORATE SOURCE: Division of Molecular Physiology, School of Life Sciences, Dundee University, Wellcome Trust Biocentre, Dundee, DD1 5EH Scotland, UK.
CONTRACT NUMBER: AR-41438 (NIAMS)
SOURCE: American journal of physiology. Endocrinology and metabolism, (2002 Jul) 283 (1) E178-86.
Journal code: 100901226. ISSN: 0193-1849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020618
Last Updated on STN: 20020712
Entered Medline: 20020710

AB The effects of endurance training on the response of **muscle AMP-activated** protein **kinase** (AMPK) and acetyl-CoA carboxylase (ACC) to moderate treadmill exercise were examined. In red quadriceps, there was a large activation of alpha 2-AMPK and inactivation of ACC in response to exercise. This response was greatly reduced after training, probably because of reduced metabolic stress. In white quadriceps, there were no effects of exercise on AMPK or ACC, but alpha 2-activity was higher after training because of increased phosphorylation of Thr(172). In soleus, there were small increases in alpha 2-activity during exercise that were not affected by training. The expression of all seven AMPK subunit isoforms was also examined. The beta 2- and gamma 2-isoforms were most highly expressed in white quadriceps, and gamma 3 was expressed in red quadriceps and soleus. There was a threefold increase in expression of gamma 3 after training in red quadriceps only. Our results suggest that gamma 3 might have a special role in the adaptation to endurance exercise in muscles utilizing oxidative metabolism.

L6 ANSWER 21 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:943313 HCAPLUS
DOCUMENT NUMBER: 138:365893
TITLE: Exercise and skeletal **muscle AMP-activated** protein **kinase**
AUTHOR(S): Hayashi, Tatsuya; Tanaka, Satsuki; Toyoda, Taro; Nakao, Kazuwa
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan
SOURCE: Naibunpi, Tonyobyoka (2002), 15(2), 111-117
CODEN: NATOFF; ISSN: 1341-3724
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review, on the activation of AMP-activated protein kinase (AMP kinase) in skeletal muscle during exercise and physiol. function of AMP kinase, discussing muscle contraction in activation of insulin-independent glucose transport; correlation between AMP kinase and insulin-independent glucose transport; activation of AMP kinase in **human** skeletal muscle; AMP kinase activation in promotion of insulin sensitivity; and role of AMP kinase in fatty acid oxidation during exercise.

L6 ANSWER 22 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 9
ACCESSION NUMBER: 2002:322719 BIOSIS
DOCUMENT NUMBER: PREV200200322719
TITLE: Reduced glucose use but abolished increases in **human** skeletal **muscle AMPK** alpha2 activity during prolonged exercise after short-term exercise training.
AUTHOR(S): McConell, Glenn Kevin [Reprint author]; Stepto, Nigel K. [Reprint author]; Chen, Zhi-Ping; Stephens, Terry J. [Reprint author]; Huynh, Ngan-Ngoc [Reprint author]; Canny, Benedict J. [Reprint author]; Kemp, Bruce E.
CORPORATE SOURCE: Physiology, Monash University, Wellington Road, Clayton, VIC, 3800, Australia
SOURCE: FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A31. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana,

USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jun 2002
Last Updated on STN: 5 Jun 2002

AB Exercise training attenuates the rise in skeletal muscle glucose uptake and free AMP:ATP ratio during exercise. This study examined the effect of short-term exercise training on AMP-activated protein kinase (AMPK) alpha2 activity during exercise. Five untrained subjects completed 120 min of cycling at 63% VO2 peak, then trained for 10 days, before repeating the exercise bout at the same absolute workload. Subjects rested for 72 hr before each trial while ingesting a high carbohydrate diet. Muscle glycogen content was significantly higher before exercise after training (93%, P<0.05). The significant increases in tracer-determined glucose disappearance and skeletal muscle AMP/ATP ratio during exercise were attenuated after exercise training (33% and 60%, respectively at 120 min, P<0.05), while the rate of muscle glycogen utilization during exercise was unaffected. AMPK alpha2 activity increased significantly during exercise before training (12-fold), but there was no increase during exercise after training. AMPK alpha1 activity increased significantly during exercise and this increase during exercise was significantly attenuated after training. This data suggest a dissociation between skeletal **muscle AMPK** alpha2 activity and glucose uptake during exercise in **humans**.

L6 ANSWER 23 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002218692 EMBASE
TITLE: Progressive increase in **human** skeletal **muscle AMPK**α2 activity and ACC phosphorylation during exercise.
AUTHOR: Stephens T.J.; Chen Z.-P.; Canny B.J.; Michell B.J.; Kemp B.E.; McConell G.K.
CORPORATE SOURCE: G.K. McConell, Dept. of Physiology, Monash Univ., Clayton, Vic. 3800, Australia. g.mcconell@med.monash.edu.au
SOURCE: American Journal of Physiology - Endocrinology and Metabolism, (2002) Vol. 282, No. 3 45-3, pp. E688-E694. .
Refs: 39
ISSN: 0193-1849 CODEN: AJPMD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020711
Last Updated on STN: 20020711

AB The effect of prolonged moderate-intensity exercise on **human** skeletal **muscle AMP-activated** protein **kinase** (AMPK)α1 and -α2 activity and acetyl-CoA carboxylase (ACCβ) and neuronal nitric oxide synthase (nNOSμ) phosphorylation was investigated. Seven active healthy individuals cycled for 30 min at a workload requiring 62.8 ± 1.3% of peak O(2) consumption (V(O2 peak)) with muscle biopsies obtained from the vastus lateralis at rest and at 5 and 30 min of exercise. AMPKα1 activity was not altered by exercise; however, AMPKα2 activity was significantly (P < 0.05) elevated after 5 min (.apprx.2-fold), and further elevated (P < 0.05) after 30 min (.apprx.3-fold) of exercise. ACCβ phosphorylation was increased (P < 0.05) after 5 min (.apprx.18-fold compared with rest) and increased (P < 0.05) further after 30 min of exercise (.apprx.36-fold compared with rest). Increases in AMPKα2 activity were significantly correlated with both increases in ACCβ phosphorylation and reductions in muscle glycogen content. Fat oxidation tended (P =

0.058) to increase progressively during exercise. Muscle creatine phosphate was lower ($P < 0.05$), and muscle creatine, calculated free AMP, and free AMP-to-ATP ratio were higher ($P < 0.05$) at both 5 and 30 min of exercise compared with those at rest. At 30 min of exercise, the values of these metabolites were not significantly different from those at 5 min of exercise. Phosphorylation of nNOSμ was variable, and despite the mean doubling with exercise, statistically significance was not achieved ($P = 0.304$). Western blots indicated that AMPKα2 was associated with both nNOSμ and ACCβ consistent with them both being substrates of AMPKα2 in vivo. In conclusion, AMPKα2 activity and ACCβ phosphorylation increase progressively during moderate exercise at .apprx.60% of Vo(2 peak) in **humans**, with these responses more closely coupled to muscle glycogen content than muscle AMP/ATP ratio.

L6 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:490371 HCAPLUS
DOCUMENT NUMBER: 135:209224
TITLE: AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise
AUTHOR(S): Musi, Nicolas; Fujii, Nobuharu; Hirshman, Michael F.; Ekberg, Ingvar; Froberg, Sven; Ljungqvist, Olle; Thorell, Anders; Goodyear, Laurie J.
CORPORATE SOURCE: Research Division, Joslin Diabetes Center and Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
SOURCE: Diabetes (2001), 50(5), 921-927
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin-stimulated GLUT4 translocation is impaired in people with type 2 diabetes. In contrast, exercise results in a normal increase in GLUT4 translocation and glucose uptake in these patients. Several groups have recently hypothesized that exercise increases glucose uptake via an insulin-independent mechanism mediated by the activation of AMP-activated protein kinase (AMPK). If this hypothesis is correct, people with type 2 diabetes should have normal AMPK activation in response to exercise. Seven subjects with type 2 diabetes and eight matched control subjects exercised on a cycle ergometer for 45 min at 70% of maximum workload. Biopsies of vastus lateralis muscle were taken before exercise, after 20 and 45 min of exercise, and at 30 min postexercise. Blood glucose concns. decreased from 7.6 to 4.77 mmol/l with 45 min of exercise in the diabetic group and did not change in the control group. Exercise significantly increased AMPK α2 activity 2.7-fold over basal at 20 min in both groups and remained elevated throughout the protocol, but there was no effect of exercise on AMPK α1 activity. Subjects with type 2 diabetes had similar protein expression of AMPK α1, α2, and β1 in muscle compared with control subjects. AMPK α2 was shown to represent approx. two-thirds of the total α mRNA in the muscle from both groups. In conclusion, people with type 2 diabetes have normal exercise-induced AMPK α2 activity and normal expression of the α1, α2 and β1 isoforms. Pharmacol. activation of AMPK may be an attractive target for the treatment of type 2 diabetes.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:275468 BIOSIS
DOCUMENT NUMBER: PREV200100275468
TITLE: AMP kinase in vascular smooth muscle.
AUTHOR(S): Rubin, Leona J. [Reprint author]; Jones, Allan W. [Reprint

author]; Magliola, Lawrence [Reprint author]; Price, Elmer M. [Reprint author]
CORPORATE SOURCE: University of Missouri, Columbia, MO, 65211, USA
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A457. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jun 2001
Last Updated on STN: 19 Feb 2002

AB AMP kinase (AMPK) is a highly conserved protein and considered to be a cellular metabolic sensor. In skeletal and cardiac **muscle**, **AMPK** is activated by exercise and/or hypoxia, and stimulates metabolic pathways that increase ATP and inhibits synthetic pathways that utilize ATP. We hypothesized that AMPK also exists in vascular smooth muscle (SM). To verify AMPK expression in vascular SM, mRNA was extracted from 1) freshly dissociated porcine coronary SM cells, 2) endothelial denuded coronary rings, 3) endothelial denuded carotid artery segments and 4) heart (positive control). mRNA was subjected to RT-PCR using primers chosen from a region of the **human** AMPK sequence (ACU06454) which had maximal sequence homology to rat AMPK. Nucleotide sequence analysis of the expected 311bp product confirmed its identity as AMPK. Incubation of coronary rings (0.5-1.0mm OD) in 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR, 2mM), an activator of AMPK; increased glucose uptake under normal (O2/10mM glucose) and metabolically depressed (N2/10mM 2-deoxyglucose (2-DG)) conditions. Coronary rings, preloaded with (3H)-adenosine exhibited minimal loss of label under normal metabolic conditions. Replacement of O2/glucose with N2/2-DG initiated a rapid increase in the rate of efflux of (3H)-adenine products which was inhibited 70% by nitrobenzylthioinosine (NBTI, 1muM, adenosine transport blocker) and 50% by AICAR (2mM). Physiological measures of tension from coronary rings indicated that AICAR (2mM) alone caused a 10.8 +- 0.9% relaxation of PGF2alpha precontracted rings but had no effect on either maximal relaxation to adenosine (0.1mM) or EC50 for adenosine relaxation (Control, 3.33 +- 0.5 muM; AICAR (2mM), 3.16 +- 0.7 muM). In contrast NBTI (1muM) significantly reduced the EC50 for adenosine relaxation (0.48 +- 0.1 muM). These data demonstrate expression of AMPK in vascular SM and implicate AMPK in regulation of SM cellular nucleotide stores.

L6 ANSWER 26 OF 30 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000505406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11052978
TITLE: AMPK signaling in contracting **human** skeletal muscle: acetyl-CoA carboxylase and NO synthase phosphorylation.
AUTHOR: Chen Z P; McConell G K; Michell B J; Snow R J; Canny B J; Kemp B E
CORPORATE SOURCE: St. Vincent's Institute of Medical Research, St. Vincent's Hospital, Fitzroy, Victoria 3065, Australia.
SOURCE: American journal of physiology. Endocrinology and metabolism, (2000 Nov) 279 (5) E1202-6.
Journal code: 100901226. ISSN: 0193-1849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001109

AB AMP-activated protein kinase (AMPK) is a metabolic stress-sensing protein kinase responsible for coordinating metabolism and energy demand. In rodents, exercise accelerates fatty acid metabolism, enhances glucose uptake, and stimulates nitric oxide (NO) production in skeletal muscle. AMPK phosphorylates and inhibits acetyl-coenzyme A (CoA) carboxylase (ACC) and enhances GLUT-4 translocation. It has been reported that **human** skeletal muscle malonyl-CoA levels do not change in response to exercise, suggesting that other mechanisms besides inhibition of ACC may be operating to accelerate fatty acid oxidation. Here, we show that a 30-s bicycle sprint exercise increases the activity of the **human** skeletal **muscle AMPK**-alpha1 and -alpha2 isoforms approximately two- to threefold and the phosphorylation of ACC at Ser(79) (AMPK phosphorylation site) approximately 8.5-fold. Under these conditions, there is also an approximately 5.5-fold increase in phosphorylation of neuronal NO synthase-mu (nNOSmu;) at Ser(1451). These observations support the concept that inhibition of ACC is an important component in stimulating fatty acid oxidation in response to exercise and that there is coordinated regulation of nNOSmu to protect the muscle from ischemia/metabolic stress.

L6 ANSWER 27 OF 30 EMBASE

ACCESSION NUMBER: 2000422534 EMBASE
TITLE: AMPK signaling in contracting **human** skeletal muscle: Acetyl-CoA carboxylase and NO synthase phosphorylation.
AUTHOR: Chen Z.-P.; McConell G.K.; Michell B.J.; Snow R.J.; Canny B.J.; Kemp B.E.
CORPORATE SOURCE: B.E. Kemp, St. Vincent's Inst. of Med. Res., St. Vincent's Hospital, 41 Victoria Parade, Fitzroy, Vic. 3065, Australia. kemp@ariel.ucs.unimelb.edu.au
SOURCE: American Journal of Physiology - Endocrinology and Metabolism, (2000) Vol. 279, No. 5 42-5, pp. E1202-E1206. . Refs: 31
ISSN: 0193-1849 CODEN: AJPMD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20001214
Last Updated on STN: 20001214

AB AMP-activated protein kinase (AMPK) is a metabolic stress-sensing protein kinase responsible for coordinating metabolism and energy demand. In rodents, exercise accelerates fatty acid metabolism, enhances glucose uptake, and stimulates nitric oxide (NO) production in skeletal muscle. AMPK phosphorylates and inhibits acetyl-coenzyme A (CoA) carboxylase (ACC) and enhances GLUT-4 translocation. It has been reported that **human** skeletal muscle malonyl-CoA levels do not change in response to exercise, suggesting that other mechanisms besides inhibition of ACC may be operating to accelerate fatty acid oxidation. Here, we show that a 30-s bicycle sprint exercise increases the activity of the **human** skeletal **muscle AMPK**-α1 and -α2 isoforms approximately two- to threefold and the phosphorylation of ACC at Ser79 (AMPK phosphorylation site) .apprx.8.5-fold. Under these conditions, there is also an .apprx.5.5-fold increase in phosphorylation of neuronal NO synthase-μ (nNOSμ) at Ser1451. These observations support the concept that inhibition of ACC is an important component in stimulating fatty acid oxidation in response to exercise and that there is coordinated regulation of nNOSμ to protect the muscle from ischemia/metabolic stress.

L6 ANSWER 28 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999345668 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10409121
TITLE: AMP-activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes.
AUTHOR: Winder W W; Hardie D G
CORPORATE SOURCE: Department of Zoology, Brigham Young University, Provo, Utah 84602, USA.. william_winder@byu.edu
CONTRACT NUMBER: AR-41438 (NIAMS)
SOURCE: American journal of physiology, (1999 Jul) 277 (1 Pt 1) E1-10. Ref: 91
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990818

AB Adenosine 5'-monophosphate-activated protein kinase (AMPK) now appears to be a metabolic master switch, phosphorylating key target proteins that control flux through metabolic pathways of hepatic ketogenesis, cholesterol synthesis, lipogenesis, and triglyceride synthesis, adipocyte lipolysis, and skeletal muscle fatty acid oxidation. Recent evidence also implicates AMPK as being responsible for mediating the stimulation of glucose uptake induced by muscle contraction. In addition, the secretion of insulin by insulin secreting (INS-1) cells in culture is modulated by AMPK activation. The net effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis, and triglyceride synthesis, inhibition of adipocyte lipolysis and lipogenesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and modulation of insulin secretion by pancreatic beta-cells. In skeletal **muscle**, **AMPK** is activated by contraction. Type 2 diabetes mellitus is likely to be a disease of numerous etiologies. However, defects or disuse (due to a sedentary lifestyle) of the AMPK signaling system would be predicted to result in many of the metabolic perturbations observed in Type 2 diabetes mellitus. Increased recruitment of the AMPK signaling system, either by exercise or pharmaceutical activators, may be effective in correcting insulin resistance in patients with forms of impaired glucose tolerance and Type 2 diabetes resulting from defects in the insulin signaling cascade.

L6 ANSWER 29 OF 30 EMBASE
ACCESSION NUMBER: 1999266189 EMBASE
TITLE: AMP-activated protein kinase, a metabolic master switch: Possible roles in Type 2 diabetes.
AUTHOR: Winder W.W.; Hardie D.G.
CORPORATE SOURCE: W.W. Winder, Dept. of Zoology, 545 WIDB, Brigham Young Univ., Provo, UT 84602, United States
SOURCE: American Journal of Physiology - Endocrinology and Metabolism, (1999) Vol. 277, No. 1 40-1, pp. E1-E10. .
Refs: 91
ISSN: 0193-1849 CODEN: AJPMD
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990812
Last Updated on STN: 19990812

AB 1-10 Adenosine 5'monophosphate-activated protein kinase (AMPK) now appears to be a metabolic master switch, phosphorylating key target proteins that control flux through metabolic pathways of hepatic ketogenesis, cholesterol synthesis, lipogenesis, and triglyceride synthesis, adipocyte lipolysis, and skeletal muscle fatty acid oxidation. Recent evidence also implicates AMPK as being responsible for mediating the stimulation of glucose uptake induced by muscle contraction. In addition, the secretion of insulin by insulin secreting (INS-1) cells in culture is modulated by AMPK activation. The net effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis, and triglyceride synthesis, inhibition of adipocyte lipolysis and lipogenesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and modulation of insulin secretion by pancreatic β- cells. In skeletal **muscle**, **AMPK** is activated by contraction. Type 2 diabetes mellitus is likely to be a disease of numerous etiologies. However, defects or disuse (due to a sedentary lifestyle) of the AMPK signaling system would be predicted to result in many of the metabolic perturbations observed in Type 2 diabetes mellitus. Increased recruitment of the AMPK signaling system, either by exercise or pharmaceutical activators, may be effective in correcting insulin resistance in patients with forms of impaired glucose tolerance and Type 2 diabetes resulting from defects in the insulin signaling cascade.

L6 ANSWER 30 OF 30 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 95080410 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7988703
TITLE: Molecular cloning, expression and chromosomal localisation of **human** AMP-activated protein kinase.
AUTHOR: Beri R K; Marley A E; See C G; Sopwith W F; Aguan K; Carling D; Scott J; Carey F
CORPORATE SOURCE: Cardiovascular and Metabolism Research Department, ZENECA Pharmaceuticals, Alderley Park, Cheshire, UK.
SOURCE: FEBS letters, (1994 Dec 12) 356 (1) 117-21.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950124
Last Updated on STN: 19950124
Entered Medline: 19950111

AB A cDNA encoding rat liver AMP-activated protein kinase (AMPK) was used to isolate **human** skeletal **muscle** **AMPK** cDNA clones. **Human** AMPK cDNA is more than 90% homologous to the rat sequence and predicts a protein of molecular mass 62.3 kDa, which closely agrees with the mass observed in Western blots of **human** tissues. AMPK antibodies were also shown to immunoprecipitate AMPK from **human** liver extracts. A cDNA probe was used to identify a 9.5kb transcript in several **human** tissues and to isolate **human** genomic clones. PCR mapping of rodent/**human** hybrid cell lines localised the **human** AMPK gene to chromosome 1, and fluorescent in situ hybridisation with a **human** genomic clone was used to sub-localise the **human** AMPK gene to 1p31.

=> d his

(FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006
L1 3955 S "AMPK"

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L2          5373 S AMP (W) ACTIVATED (3W) KINASE?
L3          6016 S L1 OR L2
L4           155 S (MUSCULAR OR MUSCLE?)(W) L3
L5            66 S HUMAN AND L4
L6            30 DUP REM L5 (36 DUPLICATES REMOVED)

=> s gamma
<------User Break------>

=> s gamma and l6
L8             6 GAMMA AND L6

=> d 1-6 ibib ab

L8   ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002324857     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12067859
TITLE:              Effects of endurance training on activity and expression of
                    AMP-activated protein kinase isoforms in rat muscles.
AUTHOR:             Durante Paula E; Mustard Kirsty J; Park Soo-Hyun; Winder
                    William W; Hardie D Grahame
CORPORATE SOURCE:   Division of Molecular Physiology, School of Life Sciences,
                    Dundee University, Wellcome Trust Biocentre, Dundee, DD1
                    5EH Scotland, UK.
CONTRACT NUMBER:    AR-41438 (NIAMS)
SOURCE:             American journal of physiology. Endocrinology and
                    metabolism, (2002 Jul) 283 (1) E178-86.
                    Journal code: 100901226. ISSN: 0193-1849.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200207
ENTRY DATE:         Entered STN: 20020618
                    Last Updated on STN: 20020712
                    Entered Medline: 20020710
AB   The effects of endurance training on the response of muscle
     AMP-activated protein kinase (AMPK) and
     acetyl-CoA carboxylase (ACC) to moderate treadmill exercise were examined.
     In red quadriceps, there was a large activation of alpha 2-AMPK and
     inactivation of ACC in response to exercise. This response was greatly
     reduced after training, probably because of reduced metabolic stress. In
     white quadriceps, there were no effects of exercise on AMPK or ACC, but
     alpha 2-activity was higher after training because of increased
     phosphorylation of Thr(172). In soleus, there were small increases in
     alpha 2-activity during exercise that were not affected by training. The
     expression of all seven AMPK subunit isoforms was also examined. The beta
     2- and gamma 2-isoforms were most highly expressed in white
     quadriceps, and gamma 3 was expressed in red quadriceps and
     soleus. There was a threefold increase in expression of gamma 3
     after training in red quadriceps only. Our results suggest that
     gamma 3 might have a special role in the adaptation to endurance
     exercise in muscles utilizing oxidative metabolism.

L8   ANSWER 2 OF 6  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
     reserved on STN
ACCESSION NUMBER:   2004054106  EMBASE
TITLE:              Cloning and characterization of mouse 5'-AMP-activated
                    protein kinase .gamma.3 subunit.
AUTHOR:             Yu H.; Fujii N.; Hirshman M.F.; Pomerleau J.M.; Goodyear
                    L.J.
CORPORATE SOURCE:   L.J. Goodyear, Joslin Diabetes Center, One Joslin Place,
                    Boston, MA 02215, United States.
                    laurie.goodyear@joslin.harvard.edu
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SOURCE: American Journal of Physiology - Cell Physiology, (2004) Vol. 286, No. 2 55-2, pp. C283-C292. .
Refs: 51
ISSN: 0363-6143 CODEN: AJPCDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040220
Last Updated on STN: 20040220

AB Naturally occurring mutations in the regulatory .**gamma**.-subunit of 5'-AMP-activated protein kinase (AMPK) can result in pronounced pathological changes that may stem from increases in muscle glycogen levels, making it critical to understand the role(s) of the .**gamma**.-subunit in AMPK function. In this study we cloned the mouse AMPK.**gamma**.3 subunit and revealed that there are two transcription start sites, which result in a long form, .**gamma**.3L (AF525500) and a short form, .**gamma**.3S (AF525501). AMPK.**gamma**.3L is the predominant form in mouse and is specifically expressed in mouse skeletal muscle at the protein level. In skeletal **muscle**, AMPK.**gamma**.3 shows higher levels of expression in fast-twitch white glycolytic muscle (type IIb) compared with fast-twitch red oxidative glycolytic muscle (type IIa), whereas .**gamma**.3 is undetectable in soleus muscle, a slow-twitch oxidative muscle with predominantly type I fibers. AMPK-.**gamma**.3 can coimmunoprecipititate with both α and β AMPK subunits. Overexpression of .**gamma**.3S and .**gamma**.3L in mouse tibialis anterior muscle in vivo has no effect on α1 and α2 subunit expression and does not alter AMPKα2 catalytic activity. However, .**gamma**.3S and .**gamma**.3L overexpression significantly increases AMPKα1 phosphorylation and activity by .apprx.50%. The increase in AMPKα1 activity is not associated with alterations in glycogen accumulation or glycogen synthase expression. In conclusion, the .**gamma**.3 subunit of AMPK is highly expressed in fast-twitch glycolytic skeletal muscle, and wild-type .**gamma**.3 functions in the regulation of α1 catalytic activity, but it is not associated with changes in muscle glycogen concentrations.

L8 ANSWER 3 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:14452 BIOSIS
DOCUMENT NUMBER: PREV200600017485
TITLE: Effects of PPAR-alpha and PPAR-**gamma** agonists on **muscle AMPK** activity in patients with type 2 diabetes (T2DM).
AUTHOR(S): Bajaj, Mandeep [Reprint Author]; Suraamornkul, Swangjit; Sriwijilkamol, Apiradee; Musi, Nicolas; Defronzo, Ralph
SOURCE: Diabetes, (2005) Vol. 54, No. Suppl. 1, pp. A151. Meeting Info.: 65th Annual Meeting of the American-Diabetes-Association. San Diego, CA, USA. June 10 -14, 2005. Amer Diabet Assoc.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Dec 2005
Last Updated on STN: 21 Dec 2005

L8 ANSWER 4 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:519270 BIOSIS
DOCUMENT NUMBER: PREV200510297184
TITLE: Effects of PPAR-alpha and PPAR-**gamma** agonists on **muscle AMPK** activity and insulin

resistance in patients with type 2 diabetes mellitus.
AUTHOR(S): Bajaj, M. [Reprint Author]; Suraamornkul, S.; Sriwijilkamol, A.; Musi, N.; DeFronzo, R.
CORPORATE SOURCE: Univ Texas, Hlth Sci Ctr, Dept Med, Diabet Div, San Antonio, TX USA
SOURCE: Diabetologia, (2005) Vol. 48, No. Suppl. 1, pp. A280. Meeting Info.: 41st Annual Meeting of the European-Association-for-the-Study-of-Diabetes. Athens, GREECE. September 10 -15, 2005. European Assoc Study Diabet.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Nov 2005
Last Updated on STN: 23 Nov 2005

L8 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:152837 HCAPLUS
DOCUMENT NUMBER: 140:197419
TITLE: AMPK activity and isoform protein expression are similar in muscle of obese subjects with and without type 2 diabetes
AUTHOR(S): Hojlund, Kurt; Mustard, Kirsty J.; Staehr, Peter; Hardie, D. Grahame; Beck-Nielsen, Henning; Richter, Erik A.; Wojtaszewski, Jorgen F. P.
CORPORATE SOURCE: Diabetes Research Centre, Odense University Hospital, University of Southern Denmark and Department of Endocrinology, Odense, DK-5000, Den.
SOURCE: American Journal of Physiology (2004), 286(2, Pt. 1), E239-E244
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute or chronic activation of AMP-activated protein kinase (AMPK) increases insulin sensitivity. Conversely, reduced expression and/or function of AMPK might play a role in insulin resistance in type 2 diabetes. Thus protein expression of the seven subunit isoforms of AMPK and activities and/or phosphorylation of AMPK and acetyl-CoA carboxylase-β (ACCβ) was measured in skeletal muscle from obese type 2 diabetic and well-matched control subjects during euglycemic-hyperinsulinemic clamps. Protein expression of all AMPK subunit isoforms (α1, α2, β1, β2, . **gamma** .1, .**gamma**.2, and .**gamma**.3) in muscle of obese type 2 diabetic subjects was similar to that of control subjects. In addition, α1- and α2-associated activities of AMPK, phosphorylation of α-AMPK subunits at Thr172, and phosphorylation of ACCβ at Ser221 showed no difference between the two groups and were not regulated by physiol. concns. of insulin. These data suggest that impaired insulin action on glycogen synthesis and lipid oxidation in skeletal muscle of obese type 2 diabetic subjects is unlikely to involve changes in AMPK expression and activity.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:153608 HCAPLUS
DOCUMENT NUMBER: 139:4309
TITLE: 5'-AMP-activated protein kinase activity and subunit expression in exercise-trained **human** skeletal muscle
AUTHOR(S): Nielsen, Jakob N.; Mustard, Kirsty J. W.; Graham, Drew A.; Yu, Haiyan; MacDonald, Christopher S.; Pilegaard,

Henriette; Goodyear, Laurie J.; Hardie, D. Grahame; Richter, Erik A.; Wojtaszewski, Jorgen F. P.

CORPORATE SOURCE: Institute of Exercise and Sport Sciences, Copenhagen Muscle Research Centre, University of Copenhagen, Copenhagen, DK-2100, Den.

SOURCE: Journal of Applied Physiology (2003), 94(2), 631-641
CODEN: JAPHEV; ISSN: 8750-7587
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 5'-AMP-activated protein kinase (AMPK) has been proposed to be a pivotal factor in cellular responses to both acute exercise and exercise training. To investigate whether protein levels and gene expression of catalytic (α1, α2) and regulatory (β1, β2, . **gamma**.1, .**gamma**.2, .**gamma**.3) AMPK subunits and exercise-induced AMPK activity are influenced by exercise training status, muscle biopsies were obtained from 7 endurance exercise-trained and 7 sedentary young healthy men. The α1- and α2-AMPK mRNA contents in trained subjects were both 117 ± 2% of that in sedentary subjects (not significant), whereas mRNA for .**gamma**.3 was 61 ± 1% of that in sedentary subjects (not significant). The level of α1-AMPK protein in trained subjects was 185 ± 34% of that in sedentary subjects ($P < 0.05$), whereas the levels of the remaining subunits (α2, β1, β2, . **gamma**.1, .**gamma**.2, .**gamma**.3) were similar in trained and sedentary subjects. At the end of 20 min of cycle exercise at 80% of peak O2 uptake, the increase in phosphorylation of α-AMPK (Thr-172) was blunted in the trained group (138 ± 38% above rest) compared with the sedentary group (353 ± 63% above rest) ($P < 0.05$). Acetyl CoA-carboxylase β-phosphorylation (Ser-221), which is a marker for in vivo AMPK activity, was increased by exercise in both groups but to a lower level in trained subjects (32 ± 5 arbitrary units) than in sedentary controls (45 ± 1 arbitrary units) ($P < 0.01$). In conclusion, trained **human** skeletal muscle has increased α1-AMPK protein levels and blunted AMPK activation during exercise.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s" R41Q" or "V40I"
S" IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s " R41Q" or "V40I"
L9          23 " R41Q" OR "V40I"

=> d his

     (FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006
L1         3955 S "AMPK"
L2         5373 S AMP (W) ACTIVATED (3W) KINASE?
L3         6016 S L1 OR L2
L4          155 S (MUSCULAR OR MUSCLE?)(W) L3
L5           66 S HUMAN AND L4
L6           30 DUP REM L5 (36 DUPLICATES REMOVED)
L7      2037417 S GAMMA
L8            6 S GAMMA AND L6
L9           23 S " R41Q" OR "V40I"
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=> s l6 and l9
L10          0 L6 AND L9

=> s l3 and l9
L11          1 L3 AND L9

=> d all

L11  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2006 ACS on STN
AN   2001:208429  HCAPLUS
DN   134:248842
ED   Entered STN:  22 Mar 2001
TI   cDNA sequences encoding various human and pig AMP-
     activated protein kinase γ subunits (gene PRKAG3),
     and methods used for detecting gene PRKAG3 mutations leading to altered
     glycogen accumulation in pig muscle cells
IN   Andersson, Leif; Looft, Christian; Kalm, Ernst; Milan, Denis; Robic,
     Annie; Rogel-Gaillard, Claire; Iannuccelli, Nathalie; Gellin, Joeel; Le
     Roy, Pascale; Chardon, Patrick
PA   Institut National de la Recherche Agronomique (Inra), Fr.
SO   PCT Int. Appl., 71 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C12N015-54
     ICS  C12N015-11; C12N009-12; C12Q001-68; A01K067-027; G01N033-68
CC   7-5 (Enzymes)
     Section cross-reference(s): 3, 13, 14
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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PI   WO 2001020003         A2    20010322    WO 2000-EP9896           20000911
     WO 2001020003         A3    20010517
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2384313            AA    20010322    CA 2000-2384313          20000911
     BR 2000013890          A    20020507    BR 2000-13890            20000911
     EP 1210441             A2   20020605    EP 2000-967845           20000911
     EP 1210441             B1   20050413
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL
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     AU 781744              B2   20050609    AU 2000-77864            20000911
     ES 2239618             T3   20051001    ES 2000-967845           20000911
PRAI EP 1999-402236         A    19990910
     EP 2000-401388         A    20000518
     WO 2000-EP9896         W    20000911
CLASS
 PATENT NO.          CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2001020003       ICM    C12N015-54
                     ICS    C12N015-11; C12N009-12; C12Q001-68; A01K067-027;
                            G01N033-68
                     IPCI   C12N0015-54 [ICM,7]; C12N0015-11 [ICS,7]; C12N0009-12
                            [ICS,7]; C12Q0001-68 [ICS,7]; A01K0067-027 [ICS,7];
                            G01N0033-68 [ICS,7]
                     ECLA   C12N009/12B1
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CA 2384313	IPCI	C12N0015-54 [ICM,7]; A01K0067-027 [ICS,7]; C12N0015-11 [ICS,7]; C12N0009-12 [ICS,7]; G01N0033-68 [ICS,7]; C12Q0001-68 [ICS,7]
BR 2000013890	IPCI	C12N0015-54 [ICM,7]; C12N0015-11 [ICS,7]; C12N0009-12 [ICS,7]; C12Q0001-68 [ICS,7]; A01K0067-027 [ICS,7]; G01N0033-68 [ICS,7]
EP 1210441	IPCI	C12N0015-54 [ICM,6]; C12N0015-11 [ICS,6]; C12N0009-12 [ICS,6]; C12Q0001-68 [ICS,6]; A01K0067-027 [ICS,6]; G01N0033-68 [ICS,6]
AT 293167	IPCI	C12N0015-54 [ICM,7]; C12N0015-11 [ICS,7]; C12N0009-12 [ICS,7]; C12Q0001-68 [ICS,7]; A01K0067-027 [ICS,7]; G01N0033-68 [ICS,7]
AU 781744	IPCI	C12N0015-54 [ICM,7]; A01K0067-027 [ICS,7]; C12N0009-12 [ICS,7]; C12N0015-11 [ICS,7]; C12Q0001-68 [ICS,7]; G01N0033-68 [ICS,7]
	ECLA	C12N009/12B1
ES 2239618	IPCI	C12N0015-54 [ICM,7]; C12N0015-11 [ICS,7]; C12N0009-12 [ICS,7]; C12Q0001-68 [ICS,7]; A01K0067-027 [ICS,7]; G01N0033-68 [ICS,7]
	ECLA	C12N009/12B1

AB The invention provides cDNA mols. encoding various muscle-specific adenosine monophosphate-activated protein kinase (**AMPK**) γ subunits isolated from human and Sus scrofa. The invention also provides: (1) primers and probes specific for said cDNA mols.; (2) recombinant vectors comprising said cDNA mols.; and (3) host cells and/or animals transformed with said vectors. The invention further provides mutants of the S. scrofa **AMPK** γ subunit, which involve an arginine→glutamine substitution at position 41, and/or a valine→isoleucine substitution at position 40. Still further, the invention provides genotyping techniques using, such as polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP), and nucleic acid hybridization for detection of a metabolic disorder (such as altered glycogen accumulation) in pigs, resulting from a mutation in the **AMPK** γ subunit gene using said primers and/or probes. The invention relates that the mol. genetic techniques can also be used to detect single nucleotide polymorphisms in the **AMPK** γ subunit gene. Finally, the invention provides for the use of said transformed cells, transgenic and/or knockout animals for screening compds. able to modulate **AMPK** activity. The cDNA sequences, as well as the corresponding amino acid sequences of various forms of **AMPK** γ subunits from human and S. scrofa are provided. The invention designated PRKAG3 as the gene encoding the muscle-specific **AMPK** γ subunit, and provides evidence that PRKAG3 is identical to the RN gene, a gene found associated with high muscular content of glycogen. The invention also provides evidence that the **R41Q** substitution is most likely the causative mutation in RN- animals which have an increase in muscle glycogen. The invention also discussed how identification of the RN- allele, or mutations in the PRKAG3, gene can be used to improve meat quality and/or breeding in the pig industry.

ST cDNA sequence swine **AMP activated** protein **kinase** gamma subunit; human cDNA sequence **AMP activated** protein **kinase** gamma subunit; mutation gene PRKAG3 pig PCR hybridization primer probe; genotyping mutation detection pig gene PRKAG3 primer; carbohydrate metabolic disorder pig gene PRKAG3 mutation detection; glycogen accumulation muscle pig gene PRKAG3 mutation detection

IT Protein motifs
(CBS domain; detection and correlation to altered glycogen accumulation of mutations in pig **AMP-activated** protein **kinase**)

IT Primers (nucleic acid)
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); FFD (Food or feed use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(DNA; primers and probes specific for **AMP-activated** protein **kinase** gene PRKAG3, and their use in genotyping and detecting mutations)

IT Gene, animal
RL: ANT (Analyte); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(PRKAG3; genotyping of pig PRKAG3 gene for identifying pigs with mutations in **AMP-activated** protein **kinase** which can alter glycogen content)

IT Phenotypes
(**R41Q** missense substitution in pig **AMP-activated** protein **kinase** exclusively associated with RN- phenotype, an increase of glycogen content, inducing increased glycolytic potential of skeletal muscle)

IT Genetic vectors
(cDNA mols. encoding various human and pig **AMP-activated** protein **kinase** γ subunits, their sequences and biol. uses)

IT Mutation
(deletion; detection and correlation to altered glycogen accumulation of mutations in pig **AMP-activated** protein **kinase**)

IT Metabolism, animal
(disorder; use of mol. genetic techniques for detection of pig **AMP-activated** protein **kinase** (**AMPK**) gene mutations resulting in altered glycogen accumulation in muscular cells)

IT Carbohydrates, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(metabolic disorders; use of mol. genetic techniques for detection of pig **AMP-activated** protein **kinase** (**AMPK**) gene mutations resulting in altered glycogen accumulation in muscular cells)

IT Microsatellite DNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT Mutation
(missense, R→Q at position 41; **R41Q** missense substitution in pig **AMP-activated** protein **kinase** exclusively associated with RN- phenotype, an increase of glycogen content, inducing increased glycolytic potential of skeletal muscle)

IT Mutation
(null, knockout; animal transformed with cDNA encoding **AMP-activated** protein **kinase** (**AMPK**) or animal whereby **AMPK** is knocked out)

IT DNA
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); FFD (Food or feed use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(primer; primers and probes specific for **AMP-activated** protein **kinase** gene PRKAG3, and their use in genotyping and detecting mutations)

IT Probes (nucleic acid)
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); FFD (Food or feed use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(primers and probes specific for **AMP-activated** protein **kinase** gene PRKAG3, and their use in genotyping and detecting mutations)

IT Genetic polymorphism
(single nucleotide; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)
IT Mutation
(substitution, V→I at position 40; **V40I** substitution in **AMP-activated** protein **kinase** results in a decrease of glycogen content, and thus of glycolytic potential of skeletal muscle)
IT Animal
(transgenic; animal transformed with cDNA encoding **AMP-activated** protein **kinase** (**AMPK**) or animal whereby **AMPK** is knocked out, and use of animal for screening compds. that modulate **AMPK**)
IT Muscle
Nucleic acid hybridization
PCR (polymerase chain reaction)
RFLP (restriction fragment length polymorphism)
(use of mol. genetic techniques for detection of pig **AMP-activated** protein **kinase** (**AMPK**) gene mutations resulting in altered glycogen accumulation in muscular cells)
IT Drug screening
(use of transformed and/or transgenic animals for screening compds. that modulate **AMPK**)
IT 74-79-3, Arginine, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**R41Q** missense substitution in pig **AMP-activated** protein **kinase** exclusively associated with RN- phenotype, an increase of glycogen content, inducing increased glycolytic potential of skeletal muscle)
IT 330694-21-8
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(RFLP marker NRAMP1-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)
IT 330694-22-9
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(RFLP marker NRAMP1-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)
IT 330694-17-2
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SNP marker 127G63-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)
IT 330694-18-3
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SNP marker 127G63-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)
IT 330694-15-0
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SNP marker CMKAR2-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)
IT 330694-16-1
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(SNP marker CMKAR2-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-19-4
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SNP marker VIL1-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-20-7
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SNP marker VIL1-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 72-18-4, Valine, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**V40I** substitution in **AMP-activated** protein **kinase** results in a decrease of glycogen content, and thus of glycolytic potential of skeletal muscle)

IT 287950-29-2P 287950-30-5P 330693-92-0P 330693-93-1P 330694-26-3P
RL: ADV (Adverse effect, including toxicity); BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(amino acid sequence; sequences, recombinant production and glycogen content altering mutations of various human and pig γ subunits of **AMP-activated** protein **kinase**)

IT 330694-34-3
RL: ARG (Analytical reagent use); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(forward primer AMPKG3F3; detection of **R41Q** substitution in pig **AMP-activated** protein **kinase** (**AMPK**) gene PRKAG3 using PCR and oligonucleotide ligation assay)

IT 172522-01-9P, Protein kinase **AMPK**
RL: ADV (Adverse effect, including toxicity); BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(gene PRKAG3, muscle-specific γ subunit; sequences, recombinant production and glycogen content altering mutations of various human and pig γ subunits of **AMP-activated** protein **kinase**)

IT 330694-01-4
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite H3-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-02-5
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite H3-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-13-8D, 5'-labeled with fluorescein
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS127B1-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-14-9
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES

(Uses)
(microsatellite MS127B1-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-11-6
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS337H2-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-12-7
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS337H2-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-09-2
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS482H65-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-10-5
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS482H65-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-05-8
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS4979L3-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-06-9
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS4979L3-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-03-6
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS982H1-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-04-7
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS982H1-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-07-0
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS997M35-specific forward primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 330694-08-1
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(microsatellite MS997M35-specific reverse primer; microsatellite and SNP marker-specific primers for region of pig chromosome 15 containing RN (PRKAG3) gene, and their use in genotyping and detecting mutations)

IT 269041-05-6 269041-06-7 330419-59-5 330419-60-8 330419-81-3
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; cDNA mols. encoding various human and pig **AMP-activated protein kinase** γ subunits, their sequences and biol. uses)

IT 330694-36-5D, 5'-Hex-labeled
RL: ARG (Analytical reagent use); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(probe SNPRN-A; detection of **R41Q** substitution in pig **AMP-activated protein kinase (AMPK**) gene PRKAG3 using PCR and oligonucleotide ligation assay)

IT 330694-37-6D, 5'-ROX-labeled
RL: ARG (Analytical reagent use); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(probe SNPRN-G; detection of **R41Q** substitution in pig **AMP-activated protein kinase (AMPK**) gene PRKAG3 using PCR and oligonucleotide ligation assay)

IT 330694-38-7
RL: ARG (Analytical reagent use); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(probe SNPRN-common; detection of **R41Q** substitution in pig **AMP-activated protein kinase (AMPK**) gene PRKAG3 using PCR and oligonucleotide ligation assay)

IT 330694-35-4
RL: ARG (Analytical reagent use); FFD (Food or feed use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(reverse primer AMPKG3R2; detection of **R41Q** substitution in pig **AMP-activated protein kinase (AMPK**) gene PRKAG3 using PCR and oligonucleotide ligation assay)

IT 9005-79-2, Glycogen, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(use of mol. genetic techniques for detection of pig **AMP-activated protein kinase (AMPK)** gene mutations resulting in altered glycogen accumulation in muscular cells)

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=> d his

     (FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006
L1          3955 S "AMPK"
L2          5373 S AMP (W) ACTIVATED (3W) KINASE?
L3          6016 S L1 OR L2
L4           155 S (MUSCULAR OR MUSCLE?)(W) L3
L5            66 S HUMAN AND L4
L6            30 DUP REM L5 (36 DUPLICATES REMOVED)
L7       2037417 S GAMMA
L8             6 S GAMMA AND L6
L9            23 S " R41Q" OR "V40I"
L10            0 S L6 AND L9
L11            1 S L3 AND L9

=> s "PRKAG3"
L12          154 "PRKAG3"

=> s l7 and l12
L13           87 L7 AND L12

=> s l4 and l13
L14            0 L4 AND L13
```

=> dup rem l13
PROCESSING COMPLETED FOR L13
L15 28 DUP REM L13 (59 DUPLICATES REMOVED)

=> d 1-28 ibib ab

L15 ANSWER 1 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1
ACCESSION NUMBER: 2006033564 EMBASE
TITLE: Characterization of the bovine **PRKAG3** gene: Structure, polymorphism, and alternative transcripts.
AUTHOR: Roux M.; Nizou A.; Forestier L.; Ouali A.; Leveziel H.; Amarger V.
CORPORATE SOURCE: V. Amarger, Faculte des Sciences et Techniques, Unite de Genetique Moleculaire Animale, Universite de Limoges, 123 av Albert Thomas, 87060 Limoges Cedex, France. valerie.amarger@unilim.fr
SOURCE: Mammalian Genome, (2006) Vol. 17, No. 1, pp. 83-92. . Refs: 32 ISSN: 0938-8990 CODEN: MAMGEC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20060209 Last Updated on STN: 20060209

AB The bovine **PRKAG3** gene encodes the AMPK .**gamma**.3 subunit, one isoform of the regulatory .**gamma**. subunit of the AMP-activated protein kinase (AMPK). The AMPK plays a major role in the regulation of energy metabolism and mutations affecting the genes encoding the .**gamma**. subunits have been shown to influence AMPK activity. The .**gamma**.3 subunit is involved in the regulation of AMPK activity in skeletal muscle and strongly inflences glycogen metabolism. Glycogen content in muscle is correlated to meat quality in livestock because it influences postmortem maturation process and ultimate pH. Naturally occurring mutations in the porcine **PRKAG3** gene highly affect meat quality by influencing glycogen content before slaughter. We present the characterization of the bovine **PRKAG3** gene and a polymorphism analysis in three cattle breeds. Thirty-two SNPs were identified among which 13 are in the coding region, one is in the 3' UTR, and 18 are in the introns. Five of them change an amino acid in the **PRKAG3** protein sequence. Allelic frequencies were determined in the three breeds considered, and mutant alleles affecting the coding sequence are found at a very low frequency. Alternative splicing sites were identified at two positions of the gene, introducing heterogeneity in the population of proteins translated from the gene. .COPYRGT. Springer Science+Business Media, Inc. 2006.

L15 ANSWER 2 OF 28 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN DUPLICATE 2
ACCESSION NUMBER: 2005-24640 BIOTECHDS
TITLE: Increasing an animal population's average genetic merit comprises selecting quantitative trait locus (QTL) for a selected trait and molecular genetic markers of interest for each QTL;
for use in genetic engineering
AUTHOR: WANG T; LOHUIS M M; KOJIMA C J; DU F; BYATT J C
PATENT ASSIGNEE: MONSANTO TECHNOLOGY LLC
PATENT INFO: WO 2005078133 25 Aug 2005
APPLICATION INFO: WO 2005-US2362 27 Jan 2005
PRIORITY INFO: US 2004-543034 9 Feb 2004; US 2004-543034 9 Feb 2004
DOCUMENT TYPE: Patent

LANGUAGE: English
OTHER SOURCE: WPI: 2005-571619 [58]
AB DERWENT ABSTRACT:
NOVELTY - Increasing an animal population's average genetic merit comprising selecting quantitative trait locus (QTL) for a selected trait, and molecular genetic markers of interest for each QTL for a selected trait, is new.

DETAILED DESCRIPTION - Increasing an animal population's average genetic merit comprises: (a) selecting one or more traits for which an improved genetic merit is desired; (b) selecting one or more quantitative trait locus QTL for each selected trait; (c) selecting three or more molecular genetic markers of interest for each QTL for each selected trait; (d) providing databases comprising: (i) genotype data for three or more molecular genetic markers for each selected trait, for animals in the population; (ii) data providing the pedigree for each animal in the population; and (iii) optionally, data for one or more fixed effects; and (e) using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to calculate a ranking of the animals, where the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits. INDEPENDENT CLAIMS are also included for: (1) a system, for increasing an animal population's average genetic merit for at one or more selected traits and for identifying the molecular genetic marker(s) having the higher degree of informativeness for one or more selected QTL, comprising: (i) a computer; (ii) a computer accessible database providing data on one or more QTL for each selected trait; (iii) a computer accessible database providing (individual) data, for animals in population, for three or more molecular genetic markers for each selected QTL for each selected trait; (iv) a computer accessible database providing pedigree data for animals in the population; (v) optionally, a computer accessible database providing individual data for each animal in the population for at least one fixed effect; (vi) a computer executable program capable of simultaneously evaluating the data in all databases, determining the relative informativeness for each of the molecular genetic markers and ranking the animals in the population according to their respective estimated breeding value for each of the selected traits; and (vii) a user interface including a data entry system, the user interface coupled to the computer and configured to allow the user to instruct the computer to access the available databases and use the computer program to generate output that includes an indication of the informativeness of each molecular genetic marker and a ranking of the animals according to their estimated breeding values and/or their individual estimated breeding values; (2) identifying the molecular genetic marker(s) having the highest degree of informativeness for at least one QTL; (3) evaluating an animal population's average genetic merit for a defined set of traits, where the defined traits comprise the animal's status for QTL and at least three molecular genetic markers for each QTL, the animal's pedigree; (4) identifying optimal breeding pairs in an animal population to improve a previously selected characteristic in the population; (5) enhancing one or more meat quality trait(s) in pigs; (6) a kit, for detecting the nature of one or more polymorphisms in the porcine **PRKAG3** (protein kinase, AMP-activated **gamma** -3 subunit) gene, comprising a means for detecting for detecting the polymorphism in the DNA and or RNA from the gene, where the polymorphisms are selected from an A/G at position 51, A/G at position 462, A/G at position 1011, C/T at position 1053, C/T at position 2475, A/G at position 2607, A/G at position 2906, A/G at position 2994, or C/T at position 4506, where all numbering is according to the sequence of 5888 base pairs (SEQ ID NO: 1); (7) an oligonucleotide used in the kit; (8) screening animals to identify those more likely to produce offspring exhibiting at least one improved meat quality trait; and (9) a pig offspring or a pig population produced using any of the methods, systems, or kits above.

BIOTECHNOLOGY - Preferred Method: The method further comprises using the calculated EBVs to prepare a breeding plan for the animal population that provides for optimal improvement in the genetic merit of the population. The animal population is a swineherd. The trait is selected from efficient growth traits, meat quality traits, reproduction traits, and health traits. The molecular genetic markers are selected from any polymorphism known to affect expression of the mRNA or protein from a gene, where the polymorphism is selected from SNPs, simple sequence repeats, protein point mutations, or gene isoforms. At least one molecular genetic marker is selected from those markers known to modulate a favorable phenotype. At least one of the molecular genetic markers is a marker for selected from a SNP in the porcine **PRKAG3** gene, or a polymorphism in the porcine melanocortin-4-receptor. The computer program uses an iteration-on-data (IOD) algorithm and a preconditioned conjugate gradient (PCCG) algorithm to determine the animals' ranks, where the PCCG algorithm is a variable-size block-diagonal preconditioning algorithm. The output of the computer program further comprises results that indicate the informativeness of one or more of the selected molecular genetic marker for at least one QTL and/or a calculation of the genetic closeness/proximity of one or more molecular markers to at least one QTL, where the molecular genetic markers having the highest degree of informativeness and/or closeness for at least one QTL are identified. The computer program uses a scripting feature to improve the ease of user interface. The selected molecular genetic markers comprise a marker haplotype. Identifying the molecular genetic marker(s) having the highest degree of informativeness for at least one QTL comprises selecting at least one trait for which an informative molecular genetic is desired, providing database(s) comprising data for one or more QTL for each selected trait, for animals in an animal population, providing database(s) comprising data for three or more molecular genetic markers for each selected QTL for each selected trait, for animals in an animal population, using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from all provided databases to calculate the informativeness of the provided markers, and identifying the marker(s) that is/are most informative for the selected trait(s). The method further comprises providing databases comprising: (i) data providing the pedigree for the animals in the animal population; and (ii) optionally, data for one or more fixed effects for the animals in the population. The method also further comprises using the computer program capable to performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from all provided databases to determine the informativeness of the selected markers and to calculate a ranking of the animals, where the animals are ranked according to their EBV for the selected traits. Evaluating an animal population's average genetic merit for a defined set of traits, where the defined traits comprise the animal's status for one or more QTL and at least three molecular genetic markers for each QTL, the animal's pedigree, the method comprises selecting one or more traits for evaluation, providing databases comprising: (i) data for one or more QTL for the animals in the population; (ii) data for three or more selected molecular genetic markers for each QTL, for each selected marker for the animals in the population; and (iii) data providing the pedigree for the animals in the population, using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to produce a ranking of the animals. The animals are ranked according to their EBV for the selected molecular genetic markers and, if provided, quantitative traits, and evaluating the EBVs to determine the animal population's average genetic merit for the defined set of characteristics. Identifying optimal breeding pairs in an animal population to improve a previously selected characteristic in the population comprises a selecting one or more traits for improvement, providing computer readable data for one or more QTL locus for the selected traits, providing computer readable data for at least three molecular genetic markers for each QTL for each

selected trait, where the data indicates the genetic makeup of animals in the population, with respect to the molecular genetic marker, providing computer readable data representing the pedigree for animals in the population, using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to produce a ranking of the animals, where the animals are ranked according to their EBV for the selected molecular genetic markers and, if provided, quantitative traits, and using then animal's rank to identify the optimal breeding pairs in the population. Enhancing one or more meat quality trait(s) in pigs comprises screening pigs to identify the nature of one or more SNPs stated above in the porcine **PRKAG3** gene, where the SNP(s) is/are selected from an A/G at position 51, A/G at position 462, A/G at position 1011, C/T at position 1053, C/T at position 2475, A/G at position 2607, A/G at position 2906, A/G at position 2994, or C/T at position 4506, where all numbering is according to the sequence of SEQ ID NO: 1 and identifying those having a desired allele, selecting those pigs identified as having a desired allele, and using the selected pigs as sires/dams in a breeding plan to produce offspring, where the offspring have an increase frequency of the desired allele. The presence or absence of the polymorphism is determined by a method selected from DNA sequencing, restriction fragment length polymorphism (RFLP) analysis, heteroduplex analysis, single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), PCR, real time PCR analysis (TAQMAN), temperature gradient gel electrophoresis (TGGE), primer extension, allele-specific hybridization, INVADER genetic analysis assays, enzyme linked immunosorbent assay (ELISA), or other immunoassay. At least one meat quality trait is selected from increased pH and decreased 7-day purge. Screening animals to identify those more likely to produce offspring exhibiting at least one improved meat quality trait comprises screening pigs to identify the nature of one or more SNPs cited above in the porcine **PRKAG3** gene. Preferred System: The quantitative trait locus is selected from any locus know to be associated with a known trait. The system further comprises providing computer accessible database(s) containing individual data for animals in the population for at least one fixed effect, where the computer executable program is capable of simultaneously evaluating the data in all provided databases and ranking the animals in the population according to their respective estimated breeding value for each of the selected traits. Preferred Kit: The kit comprises one or more of the following: a restriction endonuclease enzyme, a DNA polymerase, a reverse transcriptase, a buffer, deoxyribonucleotides, an oligonucleotide uses as a DNA or RNA probe, an oligonucleotide used as a primer in DNA or RNA synthesis, a fluorescent marker, and an antibody. Preferred Oligonucleotide: The oligonucleotide is selected a primers comprising any of the 16 nucleotide sequences listed in the disclosure (SEQ ID NO: 2-17).

USE - The methods, systems, and kits are useful for increasing an animal population's average genetic merit, identifying the molecular genetic marker(s) having the highest degree of informativeness for at least one QTL, evaluating an animal population's average genetic merit for a defined set of traits, identifying optimal breeding pairs in an animal population to improve a previously selected characteristic in the population, enhancing one or more meat quality trait(s) in pigs, and for screening animals to identify those more likely to produce offspring exhibiting at least one improved meat quality trait.(75 pages)

L15 ANSWER 3 OF 28 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005625557 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16306365
TITLE: Changes in Exercise-Induced Gene Expression in 5'-AMP-Activated Protein Kinase {**gamma**}3-Null and {**gamma**}3 R225Q Transgenic Mice.
AUTHOR: Barnes Brian R; Long Yun Chau; Steiler Tatiana L; Leng Ying; Galuska Dana; Wojtaszewski Jorgen F P; Andersson

Leif; Zierath Juleen R
CORPORATE SOURCE: Karolinska Institutet, Department of Surgical Sciences, Section of Integrative Physiology, von Eulers vag 4, 4th Floor, S-171 77 Stockholm, Sweden..
juleen.zierath@fyfa.ki.se
SOURCE: Diabetes, (2005 Dec) 54 (12) 3484-9.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20051129
Last Updated on STN: 20051216

AB 5'-AMP-activated protein kinase (AMPK) is important for metabolic sensing. We used AMPKgamma3 mutant-overexpressing Tg-**Prkag3**(225Q) and AMPKgamma3-knockout **Prkag3**(-/-) mice to determine the role of the AMPKgamma3 isoform in exercise-induced metabolic and gene regulatory responses in skeletal muscle. Mice were studied after 2 h swimming or 2.5 h recovery. Exercise increased basal and insulin-stimulated glucose transport, with similar responses among genotypes. In Tg-**Prkag3** (225Q) mice, acetyl-CoA carboxylase (ACC) phosphorylation was increased and triglyceride content was reduced after exercise, suggesting that this mutation promotes greater reliance on lipid oxidation. In contrast, ACC phosphorylation and triglyceride content was similar between wild-type and **Prkag3**(-/-) mice. Expression of genes involved in lipid and glucose metabolism was altered by genetic modification of AMPKgamma3. Expression of lipoprotein lipase 1, carnitine palmitoyl transferase 1b, and 3-hydroxyacyl-CoA dehydrogenase was increased in Tg-**Prkag3** (225Q) mice, with opposing effects in **Prkag3**(-/-) mice after exercise. GLUT4, hexokinase II (HKII), and glycogen synthase mRNA expression was increased in Tg-**Prkag3**(225Q) mice after exercise. GLUT4 and HKII mRNA expression was increased in wild-type mice and blunted in **Prkag3**(-/-) mice after recovery. In conclusion, the **Prkag3**(225Q) mutation, rather than presence of a functional AMPKgamma3 isoform, directly promotes metabolic and gene regulatory responses along lipid oxidative pathways in skeletal muscle after endurance exercise.

L15 ANSWER 4 OF 28 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2005604270 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16237515
TITLE: Role of AMP-activated protein kinase in the coordinated expression of genes controlling glucose and lipid metabolism in mouse white skeletal muscle.
AUTHOR: Long Y C; Barnes B R; Mahlapuu M; Steiler T L; Martinsson S; Leng Y; Wallberg-Henriksson H; Andersson L; Zierath J R
CORPORATE SOURCE: Department of Surgical Sciences, Section for Integrative Physiology, Karolinska Institute, Stockholm, Sweden.
SOURCE: Diabetologia, (2005 Nov) 48 (11) 2354-64. Electronic Publication: 2005-10-20.
Journal code: 0006777. ISSN: 0012-186X.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 20051115
Last Updated on STN: 20060127
Entered Medline: 20060126

AB AIMS/HYPOTHESIS: AMP-activated protein kinase (AMPK) regulates metabolic adaptations in skeletal muscle. The aim of this study was to investigate whether AMPK modulates the expression of skeletal muscle genes that have been implicated in lipid and glucose metabolism under fed or fasting

conditions. METHODS: Two genetically modified animal models were used: AMPK gamma3 subunit knockout mice (**Prkag3**(-/-)) and skeletal muscle-specific transgenic mice (Tg-**Prkag3**(225Q)) that express a mutant (R225Q) gamma3 subunit. Levels of mRNA transcripts of genes involved in lipid and glucose metabolism in white gastrocnemius muscles of these mice (under fed or 16-h fasting conditions) were assessed by quantitative real-time PCR. RESULTS: Wild-type mice displayed a coordinated increase in the transcription of skeletal muscle genes encoding proteins involved in lipid/oxidative metabolism (lipoprotein lipase, fatty acid transporter, carnitine palmitoyl transferase-1 and citrate synthase) and glucose metabolism (glycogen synthase and lactate dehydrogenase) in response to fasting. In contrast, these fasting-induced responses were impaired in **Prkag3**(-/-) mice. The transcription of genes involved in lipid and oxidative metabolism was increased in the skeletal muscle of Tg-**Prkag3**(225Q) mice compared with that in wild-type mice. Moreover, the expression of the genes encoding hexokinase II and 6-phosphofrucktokinase was decreased in Tg-**Prkag3**(225Q) mice after fasting. CONCLUSIONS/INTERPRETATION: AMPK is involved in the coordinated transcription of genes critical for lipid and glucose metabolism in white glycolytic skeletal muscle.

L15 ANSWER 5 OF 28 EMBASE DUPLICATE 5

ACCESSION NUMBER: 2005207470 EMBASE

TITLE: 5'-AMP-activated protein kinase regulates skeletal muscle glycogen content and ergogenics.

AUTHOR: Barnes B.R.; Glund S.; Long Y.C.; Hjalm G.; Andersson L.; Zierath J.R.

CORPORATE SOURCE: J.R. Zierath, Karolinska Institutet, Department of Surgical Sciences, Section of Integrative Physiology, von Eulers vag 4, S-171 77 Stockholm, Sweden. Juleen.Zierath@fyfa.ki.se

SOURCE: FASEB Journal, (2005) Vol. 19, No. 7, pp. 773-779. .
Refs: 31
ISSN: 0892-6638 CODEN: FAJOEC

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20050609
Last Updated on STN: 20050609

AB 5'-AMP-activated protein kinase (AMPK) activity is increased during exercise in an intensity- and glycogen-dependent manner. We previously reported that a mutation in the AMPK.**gamma**.S subunit (**Prkag3**(225Q)) increases AMPK activity and skeletal muscle glycogen content. Transfection experiments revealed the R225Q mutation is associated with high basal AMPK activity and diminished AMP dependence. Thus, the R225Q mutation can be considered a loss-of-function mutation that abolished allosteric regulation by AMP/ATP, causing increased basal AMPK activity. We used AMPK.**gamma**.S transgenic (Tg-**Prkag3**(225Q)) and knockout (**Prkag3**(-/-)) mice to determine the relationship between AMPK activity, glycogen content, and ergogenics (ability to perform work) in isolated extensor digitorum longus skeletal muscle after contractions induced by electrical stimulation. Contraction-induced AMPK activity was inversely coupled to glycogen content in wild-type and Tg-**Prkag3**(225Q) mice, but not in **Prkag3**(-/-) mice, highlighting a partial feedback control of glycogen on contraction-induced AMPK activity in the presence of a functional AMPK.**gamma**.S isoform. Skeletal muscle glycogen content was positively correlated to work performance, regardless of genotype. Thus, chronic activation of AMPK by the **Prkag3**(225Q) mutation directly influences skeletal muscle ergogenics by enhancing glycogen content. In conclusion, functional studies of the AMPK. **gamma**.S isoform further support the close connection between

glycogen content and exercise performance in skeletal muscle.

L15 ANSWER 6 OF 28 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2005518919 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16191037
TITLE: Molecular cloning and characterization of bovine **PRKAG3** gene: structure, expression and single nucleotide polymorphism detection.
AUTHOR: Yu S L; Kim J E; Chung H J; Jung K C; Lee Y J; Yoon D H; Lee S H; Choi I; Bottema C D K; Sang B C; Lee J H
CORPORATE SOURCE: Division of Animal Science and Resources, Research Center for Transgenic Cloned Pigs, Chungnam National University, Daejeon, Korea.
SOURCE: Journal of animal breeding and genetics = Zeitschrift fur Tierzuchtung und Zuchtungsbiologie, (2005 Oct) 122 (5) 294-301.
Journal code: 100955807. ISSN: 0931-2668.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 20050930
Last Updated on STN: 20060211
Entered Medline: 20060210

AB The protein kinase adenosine monophosphate-activated gamma3-subunit (**PRKAG3**) gene encodes a muscle-specific isoform of the regulatory **gamma**-subunit of adenosine monophosphate-activated protein kinase, which plays a key role in regulating energy homeostasis in eucaryotes. It is well known that mutations in the **PRKAG3** gene affect high glycogen content in the porcine skeletal muscle and, consequently, meat quality. The genomic structure and sequence of the bovine **PRKAG3** were analysed from a Korean cattle BAC clone. The bovine **PRKAG3** gene comprises 13 exons and spans approximately 6.8 kb on BTA2. From 5' and 3'-rapid amplification of cDNA ends experiments, the full-length cDNA of bovine **PRKAG3** has been identified, encoding a deduced protein of 465 amino acids. Two splice isoforms, generated by the alternative splicing of exon 2, were also identified. Northern blot analysis demonstrated that, similar to other species, the bovine **PRKAG3** transcript was only expressed in skeletal muscle. Seven single nucleotide polymorphisms, including two previously identified variants, were detected in four Bos taurus cattle breeds. The bovine **PRKAG3** gene described in this study may be involved in muscle-related genetic diseases or meat quality traits in cattle.

L15 ANSWER 7 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:450798 BIOSIS
DOCUMENT NUMBER: PREV200510240069
TITLE: Mechanisms of water-holding capacity of meat: The role of postmortem biochemical and structural changes.
AUTHOR(S): Huff-Lonergan, Elisabeth [Reprint Author]; Lonergan, Steven M.
CORPORATE SOURCE: Iowa State Univ, Dept Anim Sci, Ames, IA 50011 USA
elonerga@iastate.edu
SOURCE: Meat Science, (SEP 2005) Vol. 71, No. 1, pp. 194-204.
CODEN: MESCDN. ISSN: 0309-1740.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Nov 2005
Last Updated on STN: 3 Nov 2005

AB Unacceptable water-holding capacity costs the meat industry millions of dollars annually. However, limited progress has been made toward understanding the mechanisms that underlie the development of drip or

purge. It is clear that early postmortem events including rate and extent of pH decline, proteolysis and even protein oxidation are key in influencing the ability of meat to retain moisture. Much of the water in the muscle is entrapped in structures of the cell, including the intra- and extramyofibrillar spaces; therefore, key changes in the intracellular architecture of the cell influence the ability of muscle cells to retain water. As rigor progresses, the space for water to be held in the myofibrils is reduced and fluid can be forced into the extramyofibrillar spaces where it is more easily lost as drip. Lateral shrinkage of the myofibrils occurring during rigor can be transmitted to the entire cell if proteins that link myolibrils together and myofibrils to the cell membrane (such as desmin) are not degraded. Limited degradation of cytoskeletal proteins may result in increased shrinking of the overall muscle cell, which is ultimately translated into drip loss. Recent evidence suggests that degradation of key cytoskeletal proteins by calpain proteinases has a role to play in determining water-holding capacity. This review will focus on key events in muscle that influence structural changes that are associated with water-holding capacity.

L15 ANSWER 8 OF 28 EMBASE DUPLICATE 7

ACCESSION NUMBER: 2004416652 EMBASE

TITLE: The 5'-AMP-activated protein kinase .**gamma**.3 isoform has a key role in carbohydrate and lipid metabolism in glycolytic skeletal muscle.

AUTHOR: Barnes B.R.; Marklund S.; Steiler T.L.; Walter M.; Hjalm G.; Amarger V.; Mahlapuu M.; Leng Y.; Johansson C.; Galuska D.; Lindgren K.; Abrink M.; Stapleton D.; Zierath J.R.; Andersson L.

CORPORATE SOURCE: J.R. Zierath, Dept. of Surgical Sciences, Section for Integrative Physiology, Karolinska Institute, von Eulers vag 4, SE-171 77 Stockholm, Sweden. Juleen.Zierath@fyfa.ki.se

SOURCE: Journal of Biological Chemistry, (10 Sep 2004) Vol. 279, No. 37, pp. 38441-38447. .
Refs: 38
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041018
Last Updated on STN: 20041018

AB 5'-AMP-activated protein kinase (AMPK) is a metabolic stress sensor present in all eukaryotes. A dominant missense mutation (R225Q) in pig **PRKAG3**, encoding the muscle-specific .**gamma**.3 isoform, causes a marked increase in glycogen content. To determine the functional role of the AMPK .**gamma**.3 isoform, we generated transgenic mice with skeletal muscle-specific expression of wild type or mutant (225Q) mouse .**gamma**.3 as well as **Prkag3** knock-out mice. Glycogen resynthesis after exercise was impaired in AMPK .**gamma** .3 knock-out mice and markedly enhanced in transgenic mutant mice. An AMPK activator failed to increase skeletal muscle glucose uptake in AMPK .**gamma**.3 knock-out mice, whereas contraction effects were preserved. When placed on a high fat diet, transgenic mutant mice but not knock-out mice were protected against excessive triglyceride accumulation and insulin resistance in skeletal muscle. Transfection experiments reveal the R225Q mutation is associated with higher basal AMPK activity and diminished AMP dependence. Our results validate the muscle-specific AMPK .**gamma**.3 isoform as a therapeutic target for prevention and treatment of insulin resistance.

L15 ANSWER 9 OF 28 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 8

ACCESSION NUMBER: 2004335490 EMBASE
TITLE: UDP-glucose pyrophosphorylase is upregulated in carriers of the porcine RN(-) mutation in the AMP-activated protein kinase.
AUTHOR: Hedegaard J.; Horn P.; Lametsch R.; Moller H.S.; Roepstorff P.; Bendixen C.; Bendixen E.
CORPORATE SOURCE: Dr. E. Bendixen, Department of Food Sciences, Danish Inst. of Agric. Sciences, P.O. Box 50, DK-8830 Tjele, Denmark. Emoke.Bendixen@agrsci.dk
SOURCE: Proteomics, (2004) Vol. 4, No. 8, pp. 2448-2454. .
Refs: 40
ISSN: 1615-9853 CODEN: PROTC7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040819
Last Updated on STN: 20040819

AB The AMP-activated protein kinase (AMPK) plays a key role in the regulation of energy metabolism in eukaryotic cells acting as a metabolic sensor. In its activated form AMPK inhibits ATP consuming pathways and stimulates ATP generating pathways. A dominant mutation, denoted RN(-), in the porcine **PRKAG3** gene, encoding the regulatory .**gamma**.3 subunit of AMPK, results in hyperaccumulation of glycogen in glycolytic skeletal muscle cells. To study the effects of this mutation on protein expression patterns in skeletal muscle, comparative proteome analysis of muscle samples from 12 animals (6 rn (+)/rn (+) and 6 RN(-)/rn (+)) was performed. The major finding of the proteome analysis was that the key enzyme in the synthesis of glycogen, UDP-glucose pyrophosphorylase, was significantly up-regulated in RN(-) carriers. This observation was subsequently supported by studies of enzyme activity and Northern blot analysis. Furthermore, the expression patterns of enzymes related to glycolysis and the citric acid cycle were also affected. Our data suggests that hyperaccumulation of glycogen mediated by the RN(-) mutation is due to an increased synthesis of glycogen.

L15 ANSWER 10 OF 28 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 2004133221 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15025572
TITLE: Determination of PRKAG1 coding sequence and mapping of PRKAG1 and PRKAG2 relatively to porcine back fat thickness QTL.
AUTHOR: Demeure O; Liaubet L; Riquet J; Milan D
CORPORATE SOURCE: Laboratoire de Genetique Cellulaire, INRA, BP 27, 31326 Castanet-Tolosan, France.
SOURCE: Animal genetics, (2004 Apr) 35 (2) 123-5.
Journal code: 8605704. ISSN: 0268-9146.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040318
Last Updated on STN: 20040526
Entered Medline: 20040525

AB PRKAG1, PRKAG2 and **PRKAG3** encode three isoforms of AMP-activated protein kinase **gamma** chain. A major effect on meat quality and a medium effect on back fat thickness of the RN- mutation in the **PRKAG3** gene has previously been reported. We have now mapped PRKAG1 and PRKAG2 at expected locations on SSC5 and SSC18 by analysis of radiation hybrids (IMpRH panel). PRKAG2 has been mapped in a region where

no quantitative trait loci (QTL) has been reported. PRKAG1 has been mapped close to (but probably outside) a region containing a QTL influencing fatness traits. We have determined the full coding sequence of PRKAG1. No missense mutation was identified when comparing the coding sequence of one Meishan and one Large White boars. Further work is, however, required to determine if a polymorphism in PRKAG1 could be responsible for a part of the variability observed on fatness traits.

L15 ANSWER 11 OF 28 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
DUPLICATE 10
ACCESSION NUMBER: 2003-24128 BIOTECHDS
TITLE: New transgenic non-human animals expressing an AMP-activated protein kinase **gamma** 3 subunit, useful as models for improving treatment, prevention or diagnosis of diseases related to energy metabolism, e.g. obesity or type 2 diabetes ;

involving vector-mediated gene transfer and expression in host cell for use in disease diagnosis and prevention
AUTHOR: ANDERSSON L; MARKLUND S
PATENT ASSIGNEE: AREXIS AB
PATENT INFO: WO 2003063586 7 Aug 2003
APPLICATION INFO: WO 2003-IB912 31 Jan 2003
PRIORITY INFO: US 2002-353430 1 Feb 2002; US 2002-353430 1 Feb 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-663404 [62]
AB DERWENT ABSTRACT:
NOVELTY - A transgenic non-human animal having integrated within its genome a transgene or a nucleic acid encoding an AMP-activated protein kinasegamma3 subunit or its variant, where the nucleic acid is operably linked to a regulatory element, is new.

DETAILED DESCRIPTION - The transgene has a nucleotide sequence that hybridizes under stringent hybridization conditions with a nucleic acid having a nucleotide sequence complementary to a fully defined sequence of 1470 base pairs (N1) given in the specification, where the sequence encodes an AMP-activated protein kinasegamma3 subunit or its variant, and where the transgene is operably linked to a promoter that drives expression in skeletal muscle. INDEPENDENT CLAIMS are included for the following: (1) an expression construct comprising a regulatory element operably linked to a nucleotide sequence having at least 75% sequence identity to the nucleotide sequence of N1, or a nucleotide sequence encoding a polypeptide having at least 75% sequence identity to a fully defined sequence of 489 amino acids (P1) given in the specification, or its portion, where the regulatory element is capable of mediating expression in skeletal muscle; (2) making a transgenic non-human animal cited above, comprising introducing the expression construct of (1) into an ovum, an embryo, or embryonic stem cells of a non-human animal; and (3) identifying a compound or composition for treating or preventing a disease related to energy metabolism, comprising: (a) administering a test compound or test composition to the transgenic non-human animal cited above, and evaluating the effect of the test compound or test composition on the energy metabolism of the transgenic non-human animal, where the test compound or test composition is identified as effective for the treatment or prevention of the disease related to energy metabolism if energy metabolism is altered; or (b) contacting a test compound or test composition with an organ, a tissue or cells derived from the transgenic non-human animal, and evaluating the effect of the test compound or test composition on the energy metabolism on the organ, tissue or cells, where the test compound or test composition is identified as effective for the treatment or prevention of the disease related to energy metabolism if energy metabolism is altered.

BIOTECHNOLOGY - Preferred Transgenic Animal: The transgenic non-human animal has an elevated glycogen content in skeletal muscle, and is selected from the group of mice, rats, rabbits, cats, dogs and pigs.

The transgenic non-human animal is preferably a mouse or a pig. The transgene hybridizes under highly stringent conditions. The nucleic acid comprises a nucleotide sequence encoding a polypeptide having at least 75% sequence identity to the sequence of P1, a fully defined sequence of 489 amino acids (P2) given in the specification, or to a fragment of P1 or P2 at least 200 amino acids in length. The nucleic acid encodes a polypeptide having the amino acid sequence of P1 or P2, or an R225Q variant of the sequence of P1 or P2. The nucleic acid sequence comprises the nucleotide sequence of N1, a fully defined sequence of 1518 (N2) or 9100 (N3) base pairs given in the specification, a codon 225 variant of the sequence of N1 or N3, or a nucleotide sequence corresponding to the mouse **Prkag3** gene. The regulatory element is a muscle specific regulatory element, such as a myosin light chain promoter, a myosin heavy chain promoter, a skeletal alpha actin promoter, a creatine kinase promoter, or an aldolase A promoter. Preferred Method: In making a transgenic non-human animal, the expression construct is microinjected into the ovum or embryo, or into embryonic stem cells, of the non-human animal. The expression construct is electroporated into the embryonic stem cells. In identifying a compound or composition for treating or preventing a disease related to energy metabolism, the tissue is skeletal muscle and the cells are muscle cells.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic. No biological data given.

MECHANISM OF ACTION - None given.

USE - The transgenic non-human animals are useful as models for improving treatment, prevention or diagnosis of diseases related to energy metabolism, or for identifying a compound or composition for treating or preventing a disease related to energy metabolism, e.g. obesity, dyslipidemia, insulin resistance syndrome, or type 2 diabetes. The expression constructs are useful for making transgenic non-human animals. (46 pages)

L15 ANSWER 12 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2003:610488 HCAPLUS
DOCUMENT NUMBER:	139:160792
TITLE:	Human AMP-activated kinase (AMPK) .**gamma**.3 subunit gene **Prkag3** promoter and uses thereof
INVENTOR(S):	Svensson, Thomas
PATENT ASSIGNEE(S):	Arexis AB, Swed.
SOURCE:	PCT Int. Appl., 53 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003064465	A2	20030807	WO 2003-IB762	20030131
WO 2003064465	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2474005	AA	20030807	CA 2003-2474005	20030131
EP 1474520	A2	20041110	EP 2003-734809	20030131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
US 2005155091 A1 20050714 US 2003-503039 20030131
PRIORITY APPLN. INFO.: US 2002-353429P P 20020201
WO 2003-IB762 W 20030131

AB The invention provides an isolated promoter of human **Prkag3**, which encodes AMP-activated kinase (AMPK) subunit .**gamma**.3. **Prkag3** gene is muscle-specific and plays a key role in the regulation of energy metabolism in skeletal muscle. Specifically, various genetic motifs in **Prkag3** promoter for various transcription activators or repressors are identified. Expression constructs containing the **Prkag3** promoter also are provided, as are methods of using such expression constructs to direct expression of a heterologous coding sequence. Host cells containing an expression construct of the invention are provided, as well as methods of using such cells to screen for compds. that transcriptionally modulate the activity of a **Prkag3** promoter.

L15 ANSWER 13 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 11

ACCESSION NUMBER: 2004:11621 BIOSIS
DOCUMENT NUMBER: PREV200400016870
TITLE: Mutation analysis of AMP-activated protein kinase subunits in inherited cardiomyopathies: Implications for kinase function and disease pathogenesis.
AUTHOR(S): Oliveira, Sandra Marisa J.; Ehtisham, Javed; Redwood, Charles S.; Ostman-Smith, Ingegerd; Blair, Edward M. [Reprint Author]; Watkins, Hugh
CORPORATE SOURCE: WTCHG, University of Oxford, Roosevelt Drive, Headington, Oxford, OX3 7BN, UK
eblair@molbiol.ox.ac.uk
SOURCE: Journal of Molecular and Cellular Cardiology, (October 2003) Vol. 35, No. 10, pp. 1251-1255. print.
ISSN: 0022-2828 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003

AB Familial hypertrophic cardiomyopathy (HCM) has been defined as a disease of the cardiac sarcomere, although sarcomeric protein mutations are not found in one third of cases. We have recently shown that HCM associated with Wolff-Parkinson-White syndrome (WPW) and conduction disease can be caused by mutations in PRKAG2, which encodes the gamma2 subunit of AMPK, an enzyme central to cellular energy homeostasis. AMPK is a heterotrimer composed of one catalytic subunit (alpha) and two regulatory subunits (beta and **gamma**). Seven known genes encode the subunit isoforms (alpha1, alpha2, beta1, beta2, gamma1, gamma2, gamma3) and all are expressed in the heart. To better understand the role of AMPK mutations in HCM/WPW and other inherited cardiomyophathies, all 7 subunit genes were screened for mutations in a panel of probands: 3 with HCM/WPW, 4 with DCM/WPW, 38 with HCM alone (in whom contractile protein mutations had not been found) and 13 with DCM alone. In total, 73 amplimers were screened in the 58 probands and a number of polymorphisms, including non-conservative substitutions, were identified. However, no further disease-causing mutations were found in any AMPK subunit gene. These results indicate that HCM with WPW is a distinct, but genetically heterogeneous, condition caused by mutations in PRKAG2 and in an unknown gene or genes, not involved in the AMPK complex. Mutations in PRKAG2 appear to specifically cause HCM with WPW and conduction disease, and not other inherited cardiomyopathies. As deleterious alleles were not found in other AMPK subunit isoforms, the mutations affecting PRKAG2 are likely to confer a specific alteration of AMPK function of particular importance in the myocardium.

L15 ANSWER 14 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on

STN

ACCESSION NUMBER: 2003:1083412 SCISEARCH
THE GENUINE ARTICLE: 750PU
TITLE: The bovine 5 ' AMPK gene family: mapping and single nucleotide polymorphism detection
AUTHOR: McKay S D; White S N; Kata S R; Loan R; Womack J E (Reprint)
CORPORATE SOURCE: Texas A&M Univ, Dept Vet Pathobiol, College Stn, TX 77843 USA (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: MAMMALIAN GENOME, (DEC 2003) Vol. 14, No. 12, pp. 853-858. ISSN: 0938-8990.
PUBLISHER: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 25
ENTRY DATE: Entered STN: 21 Dec 2003
Last Updated on STN: 21 Dec 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The 5'-AMP-activated protein kinase (AMPK) family is an ancient stress response system whose primary function is regulation of cellular ATP. Activation of AMPK, which is instigated by environmental and nutritional stresses, initiates energy-conserving measures that protect the cell by inhibition and phosphorylation of key enzymes in energy-consuming biochemical pathways. The seven genes that comprise the bovine AMPK family were mapped in cattle by using a radiation hybrid panel. The seven genes mapped to six different cattle chromosomes, each with a LOD score greater than 10.0. PRKAA1 mapped to BTA 20, PRKAA2 and PRKAB2 to BTA 3, PRKAB1 to BTA 17, PRKAG1 to BTA 5, PRKAG2 to BTA 4, and **PRKAG3** to BTA 2. Five of the seven genes mapped to regions expected from human/cattle comparative maps. PRKAB2 and **PRKAG3**, however, have not been mapped in humans. We predict these genes to he located on HSA 1 and 2, respectively. Additionally, one synonymous and one non-synonymous single nucleotide polymorphism (SNP) were detected in **PRKAG3** in Bos taurus cattle. In an effort to determine ancestral origins, various herds of mixed breed cattle as well as other ruminant species were characterized for sequence variation in this region of **PRKAG3**. Owing to the physiological importance of this gene family, we believe that its individual genes are candidate genes for conferring resistance to diseases in cattle.

L15 ANSWER 15 OF 28 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2003296312 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12825073
TITLE: Muscle glycogenosis with low phosphorylase kinase activity: mutations in PHKA1, PHKG1 or six other candidate genes explain only a minority of cases.
AUTHOR: Burwinkel Barbara; Hu Bin; Schroers Anja; Clemens Paula R; Moses Shimon W; Shin Yoon S; Pongratz Dieter; Vorgerd Matthias; Kilimann Manfred W
CORPORATE SOURCE: Institut fur Physiologische Chemie, Ruhr-Universitat Bochum, D-44780 Bochum, Germany.
SOURCE: European journal of human genetics : EJHG, (2003 Jul) 11 (7) 516-26.
Journal code: 9302235. ISSN: 1018-4813.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20030626
Last Updated on STN: 20040323
Entered Medline: 20040322

AB Muscle-specific deficiency of phosphorylase kinase (Phk) causes glycogen

storage disease, clinically manifesting in exercise intolerance with early fatiguability, pain, cramps and occasionally myoglobinuria. In two patients and in a mouse mutant with muscle Phk deficiency, mutations were previously found in the muscle isoform of the Phk alpha subunit, encoded by the X-chromosomal PHKA1 gene (MIM # 311870). No mutations have been identified in the muscle isoform of the Phk **gamma** subunit (PHKG1). In the present study, we determined Q1the structure of the PHKG1 gene and characterized its relationship to several pseudogenes. In six patients with adult- or juvenile-onset muscle glycogenosis and low Phk activity, we then searched for mutations in eight candidate genes. The coding sequences of all six genes that contribute to Phk in muscle were analysed: PHKA1, PHKB, PHKG1, CALM1, CALM2 and CALM3. We also analysed the genes of the muscle isoform of glycogen phosphorylase (PYGM), of a muscle-specific regulatory subunit of the AMP-dependent protein kinase (**PRKAG3**), and the promoter regions of PHKA1, PHKB and PHKG1. Only in one male patient did we find a PHKA1 missense mutation (D299V) that explains the enzyme deficiency. Two patients were heterozygous for single amino-acid replacements in PHKB that are of unclear significance (Q657K and Y770C). No sequence abnormalities were found in the other three patients. If these results can be generalized, only a fraction of cases with muscle glycogenosis and a biochemical diagnosis of low Phk activity are caused by coding, splice-site or promoter mutations in PHKA1, PHKG1 or other Phk subunit genes. Most patients with this diagnosis probably are affected either by elusive mutations of Phk subunit genes or by defects in other, unidentified genes.

L15 ANSWER 16 OF 28 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2003039119 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12546692
TITLE: Identification and characterization of AMPK **gamma** 3 mutations in the pig.
AUTHOR: Andersson L
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Box 597, S-751 24 Uppsala, Sweden.. Leif.Andersson@bmc.uu.se
SOURCE: Biochemical Society transactions, (2003 Feb) 31 (Pt 1) 232-5. Ref: 22
Journal code: 7506897. ISSN: 0300-5127.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030128
Last Updated on STN: 20031111
Entered Medline: 20031110

AB The RN(-) (rendement Napole, French for Napole yield) phenotype is common in Hampshire pigs and is characterized by a 70% increase in glycogen content in skeletal muscle and large effects on meat characteristics (pH, water content, technological yield and lean meat content). The phenotype is controlled by an autosomal dominant allele designated RN (-). The protein kinase AMP-activated **gamma** 3 subunit gene, **PRKAG3**, which encodes the **gamma** 3 isoform of AMP-activated protein kinase (AMPK), was identified as the causative gene for this phenotype by a pure positional cloning approach. There are now several lines of evidence supporting our interpretation that the RN(-) phenotype is caused by a missense mutation (Arg(200)-->Gln) in **PRKAG3**. Recent data from another group have revealed the presence of a third functional allele at the **PRKAG3** locus, probably caused by a Val(199)-->Ile missense mutation. This allele has opposite effects compared with RN, as it is associated with a low glycogen content. We have confirmed the phenotypic effect of this third allele in a

meat-quality study of a Hampshire/Landrace intercross. A physiological characterization of RN(-) carriers and normal pigs showed that the RN(-) pigs utilized glycogen during exercise to the same extent as normal pigs and they showed a significantly faster resynthesis of glycogen after exercise. The results strongly suggest that the Arg(200)-->Gln substitution is not associated with a defect in glycogen degradation, but rather with an increased glucose uptake in skeletal muscle.

L15 ANSWER 17 OF 28 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2004080675 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14970705
TITLE: Molecular characterization and mutational screening of the **PRKAG3** gene in the horse.
AUTHOR: Park H B; Marklund S; Jeon J T; Mickelson J R; Valberg S J; Sandberg K; Andersson L
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden.
SOURCE: Cytogenetic and genome research, (2003) 102 (1-4) 211-6. Journal code: 101142708. ISSN: 1424-859X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040219
Last Updated on STN: 20040608
Entered Medline: 20040607

AB The **PRKAG3** gene encodes a muscle-specific isoform of the regulatory **gamma** subunit of AMP-activated protein kinase (AMPK). A major part of the coding **PRKAG3** sequence was isolated from horse muscle cDNA using reverse-transcriptase (RT)-PCR analysis. Horse-specific primers were used to amplify genomic fragments containing 12 exons. Comparative sequence analysis of horse, pig, mouse, human, Fugu, and zebrafish was performed to establish the exon/intron organization of horse **PRKAG3** and to study the homology among different isoforms of AMPK **gamma** genes in vertebrates. The results showed conclusively that the three different isoforms (gamma1, gamma2, and gamma3) were established already in bony fishes. Seven single nucleotide polymorphisms (SNPs), five causing amino acid substitutions, were identified in a screening across horse breeds with widely different phenotypes as regards muscle development and intended performance. The screening of a major part of the **PRKAG3** coding sequence in a small case/control material of horses affected with polysaccharide storage myopathy did not reveal any mutation that was exclusively associated with this muscle storage disease. The breed comparison revealed several potentially interesting SNPs. One of these (Pro258Leu) occurs at a residue that is highly conserved among AMPK **gamma** genes. In an SNP screening, the variant allele was only found in horse breeds that can be classified as heavy (Belgian) or moderately heavy (North Swedish Trotter, Fjord, and Swedish Warmblood) but not in light horse breeds selected for speed or racing performance (Standardbred, Thoroughbred, and Quarter horse) or in ponies (Icelandic horses and Shetland pony). The results will facilitate future studies of the possible functional significance of **PRKAG3** polymorphisms in horses.

L15 ANSWER 18 OF 28 EMBASE DUPLICATE 15
ACCESSION NUMBER: 2004103092 EMBASE
TITLE: Comparative sequence analysis of the **PRKAG3** region between human and pig: Evolution of repetitive sequences and potential new exons.
AUTHOR: Amarger V.; Erlandsson R.; Pielberg G.; Jeon J.-T.; Andersson L.

CORPORATE SOURCE: L. Andersson, Dept. Med. Biochem. and Microbiol., Uppsala University, Box 597, SE-751 24 Uppsala, Sweden. Leif.Andersson@imbim.uu.se
SOURCE: Cytogenetic and Genome Research, (2003) Vol. 102, No. 1-4, pp. 163-172. .
Refs: 28
ISSN: 1424-8581 CODEN: CGRYAJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040325
Last Updated on STN: 20040325

AB The **PRKAG3** gene encodes the .**gamma**.3 chain of AMPactivated protein kinase (AMPK). A non-conservative missense mutation in the **PRKAG3** gene causes a dominant phenotype involving abnormally high glycogen content in pig skeletal muscle. We have determined >126 kb (in 13 contigs) of porcine genomic sequence surrounding the **PRKAG3** gene and the corresponding mouse region covering the gene. A comparison of these **PRKAG3** sequences and the human sequence was conducted and used to predict evolutionarily conserved regions, including regulatory regions. A comparison of the human genomic sequence and a porcine BAC sequence containing the **PRKAG3** gene, revealed a conserved organization and the presence of three additional genes, CYP27A1 (cytochrome P450, family 27, subfamily A, polypeptide 1), STK36 (Serine Threonine Kinase 36), and the homolog of the unidentified human mRNA KIAA0173. Interspersed repetitive elements constituted 51.4 and 38.6% of this genomic region in human and pig, respectively. We were able to reliably align 12.6 kb of orthologous repeats shared between pig and human and these showed an average sequence identity of 72.4%. Our analysis revealed that the human KIAA0173 gene harbors alternative 5' untranslated exons originating from repetitive elements. This provides an obvious example how transposable elements may affect gene evolution.

L15 ANSWER 19 OF 28 EMBASE
ACCESSION NUMBER: 2004103089 EMBASE
TITLE: Study of candidate genes for glycolytic potential of porcine skeletal muscle: Identification and analysis of mutations, linkage and physical mapping and association with meat quality traits in pigs.
AUTHOR: Fontanesi L.; Davoli R.; Nanni Costa L.; Scotti E.; Russo V.
CORPORATE SOURCE: L. Fontanesi, DIPROVAL Sezione Allevamenti Z., Faculty of Agriculture, University of Bologna, Via F.lli Rosselli 107, 42100 Reggio Emilia, Italy. luca.fontanesi@stpa.unibo.it
SOURCE: Cytogenetic and Genome Research, (2003) Vol. 102, No. 1-4, pp. 145-151. .
Refs: 26
ISSN: 1424-8581 CODEN: CGRYAJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040325
Last Updated on STN: 20040325

AB Several genes (PRKAA2, PRKAB1, PRKAB2, **PRKAG3**, GAA, GYS1, PYGM, ALDOA, GPI, LDHA, PGAM2 and PKM2), chosen according to their role in the regulation of the energy balance and in the glycogen metabolism and glycolysis of the skeletal muscle, were studied. Eleven single nucleotide

polymorphisms (SNPs) were identified in six of these genes (PRKAB1, GAA, PYGM, LDHA, PGAM2 and PKM2). Allele frequencies were analyzed in seven different pig breeds for these loci and for a polymorphism already described for GPI and for three polymorphic sites already reported at the **PRKAG3** locus (T30N, G52S and I199V). Linkage mapping assigned PYGM and LDHA to porcine chromosome (SSC) 2, PKM2 to SSC7, GAA to SSC12, PRKAB1 to SSC14 and PGAM2 to SSC18. Physical mapping, obtained by somatic cell hybrid panel analysis, confirmed the linkage assignments of PRKAB1 and GAA and localized ALDOA, PRKAB2 and GYS1 to SSC3, SSC4 and SSC6, respectively. Pigs selected for the association study, for which several meat quality traits were measured, were first genotyped at the **PRKAG3** R200Q polymorphic site (RN locus), in order to exclude carriers of the 200Q allele, and then were genotyped for all the mutations considered in this work. Significant associations ($P \leq 0.001$) were observed for the **PRKAG3** T30N and G52S polymorphic sites with meat colour (L* at 24 h post mortem). PGAM2 and PKM2 were significantly associated ($P = 0.01$) with drip loss percentage and glycogen content at one hour post mortem, respectively.

L15 ANSWER 20 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:254666 BIOSIS
DOCUMENT NUMBER: PREV200400253636
TITLE: The use of haplotype information in the genetic dissection of genes affecting important traits.
AUTHOR(S): Ciobanu, D. C. [Reprint Author]
CORPORATE SOURCE: Sygen International, Berkeley, CA, USA
SOURCE: Journal of Animal Science, (2003) Vol. 81, No. Supplement 2, pp. 86. print.
Meeting Info.: American Society of Animal Science Midwestern Branch. Des Moines, IA, USA. March 17-19, 2003.
ISSN: 0021-8812 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 May 2004
Last Updated on STN: 12 May 2004

L15 ANSWER 21 OF 28 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
DUPLICATE 16

ACCESSION NUMBER: 2002-13330 BIOTECHDS
TITLE: Screening animals to determine those likely to produce larger litters and improved meat quality traits involves assaying for the presence of polymorphisms in the AMP activated protein kinase regulatory **gamma** subunit gene;
DNA polymorphism identification on protein-kinase **PRKAG3** gene, DNA sequencing and BLAST comparison
AUTHOR: ROTHSCHILD M F; CIOBANU D C; MALEK M; PLASTOW G
PATENT ASSIGNEE: UNIV IOWA STATE RES FOUND INC
PATENT INFO: WO 2002020850 14 Mar 2002
APPLICATION INFO: WO 2000-US28283 8 Sep 2000
PRIORITY INFO: US 2001-299111 18 Jun 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-393850 [42]
AB DERWENT ABSTRACT:
NOVELTY - Screening (M1-3) animals to determine those more likely to (a) produce large litters, or (b) improved meat quality traits involves assaying for presence of a genotype in the sample of genetic material obtained from animal. The genotype is characterized by polymorphism(s) in the AMP activated protein kinase regulatory **gamma** subunit (**PRKAG3**) gene.
DETAILED DESCRIPTION - Screening (M1) animals to determine those

most likely to produce larger litters involves obtaining a sample of genetic material from the animal, assaying for the presence of a genotype in the animal which is associated with the increased litter size,where the genotype is characterized by a polymorphism in the **PRKAG3** gene. Screening (M2) animals to determine those most likely to produce improved or favorable meat quality traits involves obtaining a biological sample of genetic material from the animal, assaying for the presence of a genotype in the animal which is associated with improved or favorable meat quality traits, where the genotype is characterized by a polymorphism (or a combination of at least two polymorphisms) in the **PRKAG3** gene (the polymorphism being one other than the ARG-ASN mutation at amino acid position 200). The polymorphism resulting in and characterized by an (a) amino acid of valine/isoleucine at position 199 and arginine at position 200, (b) an amino acid change of asparagine to threonine at amino acid position 30, or (c) an amino acid change of glycine to serine, or its equivalent as determined by BLAST comparison of a fully defined **PRKAG3** protein sequence of 464 amino acids (S2) as given in specification. Optionally, screening (M3) animals to determine those with a favorable combination of traits for meat quality and/or litter size, involves determining the alleles of **PRKAG3** gene present in an animal, the alleles comprising those which include one or more of the following: a polymorphic BsaHI, HpHI, or StyI site in the **PRKAG3** gene; determining the alleles of other markers for genes known to affect meat quality and/or litter size; and selecting for animals with favorable combinations of alleles and against those carrying unfavorable combinations. Also, screening animals to determine those more likely to have increased value for litter size and/or favorable meat quality traits involves obtaining a sample of genetic material from the animal; assaying the presence of a genotype in the animal which is associated with favorable litter size and/or meat quality, the genotype characterized by a combination of at least two polymorphisms in the **PRKAG3**, or by short interspersed element polymorphism in the **PRKAG3** gene. INDEPENDENT CLAIMS are also included for the following: (1) a nucleotide sequence comprising a fully defined sequence of 1873 nucleotides (I) which encodes upon expression a **PRKAG3** protein, further comprising a serine at position 52; (2) a nucleotide sequence (II) which encodes upon expression an **PRKAG3** protein comprising (a) an isoleucine or valine at position 199 and an arginine at position 200 or its equivalent of the protein, or (b) isoleucine at position 199, threonine at position 30, glycine at position 52 and arginine at position 200 or its equivalent of the protein; (3) a **PRKAG3** protein encoded by (I) or (II); and (4) identifying (M4) a genetic marker for meat quality and/or litter size in animals involves determining number of offspring produced by each female animal or the meat quality of the animal; determining the polymorphism in the **PRKAG3** or equivalent gene of each animal; the polymorphism as described above or their equivalents and associating the number of offspring produced by each female animal or meat quality with the polymorphism and thereby identifying a polymorphism for animal meat quality or litter size.

WIDER DISCLOSURE - Also disclosed is a method for assaying for protein conformational or sequence changes which occur in the presence of **PRKAG3** gene.

BIOTECHNOLOGY - Preferred Method: In (M1), the polymorphism results in an amino acid change from valine to isoleucine at amino acid number 199 of **PRKAG3** gene or its equivalent as determined by BLAST comparison of (S2); and is a transition of guanine to adenine at nucleotide position 595 or its equivalent, or is a BsaHI polymorphism. Assaying the presence of genotype in the animal is carried out by restriction fragment length polymorphism analysis, minisequencing, matrix assisted laser desorption ionization-time-of-flight (MALDI-TOF), short interspersed nuclear element (SINE), heteroduplex analysis, single-strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis, or temperature gradient gel electrophoresis. (M1)

further involves amplifying the amount of **PRKAG3** gene or its portion which contains the polymorphism. The amplification involves selecting forward and reverse sequence primers capable of amplifying a region of **PRKAG3** gene which contains a polymorphic BsaHI site. The forward and reverse primers are preferably selected from and based upon primer RNF and primer RNR. In (M2), the polymorphism resulting in and characterized by valine or isoleucine at position 199, is a transition of guanine to adenine at nucleotide position 595 or its equivalent. The assaying step involves a SINE polymorphism test, where the assay comprises amplifying the **PRKAG3** gene using primers from and based upon primer RP1F and primer PN52R2. The method further involves amplifying **PRKAG3** gene or its portion which contains the polymorphism, and includes the step of selecting primers RNF and RNR which are capable of amplifying region of **PRKAG3** gene which contains BsaHI site. The polymorphism resulting in and characterized by amino acid change of (a) Asn to Thr at amino acid position 30 of (S2), or (b) glycine to serine at amino acid position 52 of (S2) or its equivalent, is a transition of (i) adenine to cytosine at nucleotide position 89 of a fully defined **PRKAG3** gene sequence of 1873 nucleotides (S1) as given in specification or its equivalent as determined by a BLAST comparison, or StyI polymorphism; or (ii) guanine to adenine at nucleotide position 154 of (S1), or HpHI polymorphism, respectively. The genotype is assayed as described above. Assaying the presence of polymorphism of Asn to Thr at amino acid position 30 of (S2) or glycine to serine at position 52 of (S2), further includes amplifying **PRKAG3** gene or its portion which contains the polymorphism and includes selecting a forward and reverse primer e.g., primer RF1 and primer RN52R2, capable of amplifying a region of **PRKAG3** gene which contains a polymorphic StyI or HpHI site. In (M3), the determination of **PRKAG3** alleles involves determining the presence of at least one allele associated with at least one DNA marker (a microsatellite) linked either directly or indirectly to **PRKAG3** . (M4) further involves selecting animals for breeding which are predicted to have favorable meat quality or litter size by the marker. The analysis preferably involves digesting PCR amplified DNA with restriction enzyme such as BsaHI, HpHI or StyI. Preferred Nucleic Acid: (I) comprises a fully defined sequence of 1873 nucleotides, and encodes a **PRKAG3** protein having a sequence of 464 amino acids as given in specification.

USE - For screening animals e.g., pigs, to determine those most likely to exhibit improved meat quality traits, and to produce larger litters (claimed).

EXAMPLE - Several significant quantitative trait linkage (QTL) were detected on SSC15 (Malek et al., 2001) in the region where the **PRKAG3** gene was located between the markers SW1683 and SW1983. These included QTL for average glycogen content and glycolytic potential to be affected by the **PRKAG3** 200Q allele as well as the traits 24 hours ham and loin pH and 24 hours Hunter L values. The favorable allele at this QTL, which had an additive effect (the RN- mutation was dominant) was derived predominantly from the Berkshire breed. The **PRKAG3** gene was the unique candidate gene in this area, based on the recent development of the bacterial artificial chromosome (BAC) contig in the porcine RN region. First the founder animals, two Berkshire sires and nine Yorkshire dams were tested, for the published RN- substitution (R2000Q). All the founder animals had the rn+ allele (200R). By sequencing the entire coding region of the **PRKAG3** gene in BxY family founders and in four F3 individuals with extreme values for meat quality, three missense mutations were identified. These were the T30N and the I199V substitutions previously described (Milan et al., 2000) and a new missense mutation (G52S). Another non-synonymous substitution (P53L) found by Milan et al., (2000) was not found to be segregating in the founders of the BxY family where they were all 53P. Due to the lack of information on the 5' untranslated region (UTR), rapid amplification of cDNA ends (RACE) was used in order to find the complete

5' flanking sequence and gene organization in that region. An intronic short interspersed nuclear element (SINE) polymorphism was discovered starting 79bp upstream of the start codon but this was present only in three Yorkshire grandams. Based on the differences in allele frequency of each site between the founders of the intercross family, the G52S and I199V substitutions were considered as the most likely candidates for the meat quality QTL reported previously. Using the I199V substitution the **PRKAG3** gene was mapped in the BxY linkage map to a position below the broad peak(s) of the QTL for glycogen, lactate ad glycolytic potential and 24 hour pH. After adding the **PRKAG3** I199V information the map length and marker order on SSC 15 was the same as in Milan et al., (2001). Using an association analysis significant effects were found of all three of the substitutions (T30N, G52S and I199V) on average glycogen and lactate content and also on glycolytic potential on the F2 BxY population. The most significant effects were revealed for I199V substitution for most of the traits analyzed, including glycogen and lactate content and glycolytic potential measures, but also in some of the meat quality traits associated with these measures. From the F2 data, the 30T, 52G and 199I alleles were favorable in terms of meat quality. The association study revealed that the largest effects across the lines and also within lines were obtained with the I199V substitution for all the traits analyzed. Significant effects, but smaller when compared to the I199V, were revealed for the T30n substitution in five of the traits when analyzed across lines. For the G52S substitution, significant effects were identified for only two of the traits (ham pH and loin Minolta L) in across lines analysis, and a different allele was identified as favorable for those traits. Also the **PRKAG3** alleles were also shown to have a significant association with litter size in animals. The polymorphism at codon 199 of **PRKAG3** was used to genotype sows with litter size data. Two lines were utilized, corresponding to a Landrace line (A) and a Duroc Synthetic line (B) that were previously found to have an association between this polymorphism and meat quality traits. A statistically significant association was found between the genotype and litter size traits (Total number born, number born alive) for line B in the First Parity. The heterozygote was found to have the largest litter size, in addition the 11 genotype had larger litters than the 22 homozygote suggesting an advantage for sows carrying at least one copy of allele. (109 pages)

L15 ANSWER 22 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:923085 HCAPLUS
DOCUMENT NUMBER: 138:249133
TITLE: A PCR-RFLP method to identify the RN- gene in retailed pork chops
AUTHOR(S): Meadus, W. J.; MacInnis, R.; Dugan, M. E. R.; Aalhus, J. L.
CORPORATE SOURCE: Lacombe Research Centre, Agriculture and Agri-Food Canada, Lacombe, AB, T4L 1W1, Can.
SOURCE: Canadian Journal of Animal Science (2002), 82(3), 449-451
CODEN: CNJNAT; ISSN: 0008-3984
PUBLISHER: Agricultural Institute of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The RN- phenotype in swine is associated with an increase in muscle glycogen. The increased glycogen leads to increased drip and cooking loss and inferior ham quality. RN- type pork was usually identified by a biochem. measure of glycolytic potential (GP), which is an estimated sum of 2(glycogen, glucose, glucose-6-phosphate) + lactate. Recently, a mutation in the **PRKAG3** gene was reported to be the cause of the dominantly inherited RN- phenotype. This note describes a new BsrBI PCR-RFLP technique used to rapidly identify the **PRKAG3** mutation and its correlation with biochem. markers for RN- type pork. The **PRKAG3** BsrBI mutation was not found in 27% of retail pork chop samples that had

high GP values.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 23 OF 28 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
DUPLICATE 17
ACCESSION NUMBER: 2001-08298 BIOTECHDS
TITLE: New variant of the **gamma** subunit kinase for diagnosis or treatment of disorders associated with energy metabolism such as diabetes, obesity, and myopathy; for gene therapy and drug screening
AUTHOR: Andersson L; Looft C; Kalm E; Milan D; Robic A; Rogel-Gaillard C; Iannuccelli N; Gellin J; Le Roy P; Chardon P
PATENT ASSIGNEE: INRA; Andersson L; Looft C; Kalm E
LOCATION: Uppsala, Sweden; Bokelholm, Germany; Achterwehr, Germany; Paris, France.
PATENT INFO: WO 2001020003 22 Mar 2001
APPLICATION INFO: WO 2000-EP9896 11 Sep 2000
PRIORITY INFO: EP 2000-401388 18 May 2000; EP 1999-402236 10 Sep 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2001-244810 [25]
AB A **gamma** subunit (I) of a vertebrate adenosine monophosphate (AMP)-activated kinase (AMPK), in which (I) is a protein containing a sequence having at least 70% identity with a protein containing 305 amino acids fully defined is claimed. Also claimed are: a protein (II); a nucleic acid sequence (III); a nucleic acid sequence (IV); a nucleic acid fragment (V); a set of DNA primers (VI); a recombinant vector (VII); a host cell (VIII); a transgenic animal (IX); a knockout animal (X); a heterotrimeric AMPK (XI); detecting (M1) a metabolic disorder resulting from a mutation in a gene encoding (I); obtaining (M2) a pair of DNA primers; a pair of DNA primers (XII); and screening compounds able to modulate AMPK activity and energy metabolism in the absence of (I). A pair of DNA primers are useful for detecting a dysfunction of carbohydrate metabolism. A host cell, a transgenic animal or heterotrimeric AMPK are useful for screening compounds that modulate AMPK activity. A nucleic acid (III) is useful for detecting mutations in a **PRKAG3** (**gamma** subunit of AMPK) gene. (III) is useful as therapeutic for treating diabetes, obesity, cardiovascular diseases, etc. (71pp)

L15 ANSWER 24 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:763167 HCAPLUS
DOCUMENT NUMBER: 135:315318
TITLE: Variants of the human AMP-activated protein kinase **gamma**.3 subunit and their use for diagnosis of a metabolic disease
INVENTOR(S): Andersson, Leif; Luthman, Holger; Marklund, Stefan
PATENT ASSIGNEE(S): Arexis AB, Swed.
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077305	A2	20011018	WO 2001-SE765	20010406
WO 2001077305	A3	20020228		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,

LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002142310	A1	20021003	US 2001-826581	20010405
US 2004121385	A1	20040624	US 2003-705137	20031110
PRIORITY APPLN. INFO.:			US 2000-195665P	P 20000407
			US 2001-826581	B1 20010405

AB This invention relates to new variants of the .**gamma**.3 subunit of human AMP-activated protein kinase (**PRKAG3**), to genes encoding the variants, and to their use. Nucleotide and encoded amino acid sequence of **PRKAG3** variants and methods of detecting such sequence variants are described. Methods for providing risk ests. for development of a metabolic disease also are described and are based on the presence or absence of **PRKAG3** sequence variants in a biol. sample.

L15 ANSWER 25 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER:	2002:89894 BIOSIS
DOCUMENT NUMBER:	PREV200200089894
TITLE:	Wolff-Parkinson-White syndrome: A genetic disease?.
AUTHOR(S):	Doevendans, Pieter A.; Wellens, Hein J. [Reprint author]
CORPORATE SOURCE:	21 Henric van Veldekeplein, 6211 TG, Maastricht, Netherlands hwellens@xs4all.nl
SOURCE:	Circulation, (December 18-25, 2001) Vol. 104, No. 25, pp. 3014-3016. print. CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE:	Article Editorial
LANGUAGE:	English
ENTRY DATE:	Entered STN: 24 Jan 2002 Last Updated on STN: 25 Feb 2002

L15 ANSWER 26 OF 28 MEDLINE on STN DUPLICATE 18

ACCESSION NUMBER:	2001682751 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 11729159
TITLE:	Evidence for new alleles in the protein kinase adenosine monophosphate-activated **gamma**(3)-subunit gene associated with low glycogen content in pig skeletal muscle and improved meat quality.
AUTHOR:	Ciobanu D; Bastiaansen J; Malek M; Helm J; Woollard J; Plastow G; Rothschild M
CORPORATE SOURCE:	Department of Animal Science, Iowa State University, Ames, Iowa 50011, USA.
SOURCE:	Genetics, (2001 Nov) 159 (3) 1151-62. Journal code: 0374636. ISSN: 0016-6731.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200203
ENTRY DATE:	Entered STN: 20011203 Last Updated on STN: 20020320 Entered Medline: 20020319

AB Several quantitative trait loci (QTL) affecting muscle glycogen content and related traits were mapped to pig chromosome 15 using a three-generation intercross between Berkshire x Yorkshire pigs. On the basis of the QTL location the **PRKAG3** (protein kinase, AMP-activated, **gamma**(3)-subunit) gene was considered to be a good candidate for the observed effects. Differences in the

PRKAG3 gene sequences of the founder animals of the intercross were analyzed. The RN(-) mutation previously reported was not present in the cross but three missense substitutions and a polymorphic short interspersed element (SINE) were identified. To confirm the hypothesis that at least one of these mutations was associated with differences in meat quality, >1800 animals from several unrelated commercial lines were genotyped for the candidate substitutions and an association study was performed. The results demonstrate the presence of new economically important alleles of the PRKAG3 gene affecting the glycogen content in the muscle and the resulting meat quality. Haplotype analysis was shown to resolve the effects of PRKAG3 more clearly than analysis of individual polymorphisms. Because of their prevalence in the more common commercial breeds, the potential implications for the pig industry and consumers are considerably greater than the original discovery of the RN(-) mutation. Furthermore, these results illustrate that additional alleles of genes involved in major mutations may play a significant role in quantitative trait variation.

L15 ANSWER 27 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:130448 BIOSIS
DOCUMENT NUMBER: PREV200300130448
TITLE: Present state of investigations on the "acid meat" RN- gene in pigs.
Original Title: Aktualny stan badan nad genem kwasnego miesa RN- u swin..
AUTHOR(S): Janik, Andrzej [Reprint Author]
CORPORATE SOURCE: Dzial Biotechnologii, Zaklad Immuno- i Cytogenetyki Zwierzat, Instytut Zootechniki, 32-083, Balice k. Krakowa, Poland
SOURCE: Biuletyn Informacyjny Instytut Zootechniki, (2001) Vol. 39, No. 3, pp. 15-22. print.
ISSN: 0209-2492.
DOCUMENT TYPE: Article
LANGUAGE: Polish
ENTRY DATE: Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003

AB The RN- or "acid meat" gene detected in Hampshire pigs and located on the chromosome number 15 leads to a decreased technological quality due to a lower meat protein content and reduced ultimate pH (below 5.4). The latter results from an increased glycogen content in the white muscle. For cooked ham processing the yield of RN- gene carriers is 6-9.5% lower. The results of further investigations in France, Germany and Sweden revealed that the hypothetic RN- gene is a mutated form of the PRKAG3 gene, which encodes a gamma subunit of the adenosine monophosphate activated protein kinase. The mutation G-A in the R200Q codon of the PRKAG3 gene is associated with excess glycogen content in pig skeletal muscle and RN alleles.

L15 ANSWER 28 OF 28 MEDLINE on STN DUPLICATE 19

ACCESSION NUMBER: 2000280150 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10818001
TITLE: A mutation in PRKAG3 associated with excess glycogen content in pig skeletal muscle.
AUTHOR: Milan D; Jeon J T; Looft C; Amarger V; Robic A; Thelander M; Rogel-Gaillard C; Paul S; Iannuccelli N; Rask L; Ronne H; Lundstrom K; Reinsch N; Gellin J; Kalm E; Roy P L; Chardon P; Andersson L
CORPORATE SOURCE: Laboratoire de Genetique Cellulaire, Institut National de la Recherche Agronomique (INRA), 31326 Castanet-Tolosan, France.
SOURCE: Science, (2000 May 19) 288 (5469) 1248-51.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000525

AB A high proportion of purebred Hampshire pigs carries the dominant RN- mutation, which causes high glycogen content in skeletal muscle. The mutation has beneficial effects on meat content but detrimental effects on processing yield. Here, it is shown that the mutation is a nonconservative substitution (R200Q) in the **PRKAG3** gene, which encodes a muscle-specific isoform of the regulatory **gamma** subunit of adenosine monophosphate-activated protein kinase (AMPK). Loss-of-function mutations in the homologous gene in yeast (SNF4) cause defects in glucose metabolism, including glycogen storage. Further analysis of the **PRKAG3** signaling pathway may provide insights into muscle physiology as well as the pathogenesis of noninsulin-dependent diabetes mellitus in humans, a metabolic disorder associated with impaired glycogen synthesis.

```
=> e andersen l/au
E1            8     ANDERSEN KURT A/AU
E2            1     ANDERSEN KURT B/AU
E3          523 --> ANDERSEN L/AU
E4           49     ANDERSEN L A/AU
E5          291     ANDERSEN L B/AU
E6           12     ANDERSEN L BRYCE/AU
E7           45     ANDERSEN L C/AU
E8            3     ANDERSEN L CHRISTINA/AU
E9            1     ANDERSEN L CHRISTINA L/AU
E10          85     ANDERSEN L D/AU
E11           8     ANDERSEN L E/AU
E12         177     ANDERSEN L F/AU

=> s e3
L16         523 "ANDERSEN L"/AU

=> e looft c/au
E1            1     LOOFSWISSOWA H H E/AU
E2            5     LOOFT AXEL/AU
E3          138 --> LOOFT C/AU
E4            2     LOOFT C H R/AU
E5            1     LOOFT CHR/AU
E6           38     LOOFT CHRISTIAN/AU
E7            2     LOOFT D/AU
E8            2     LOOFT D J/AU
E9            3     LOOFT F/AU
E10           1     LOOFT F C/AU
E11          63     LOOFT F J/AU
E12           1     LOOFT F J 3RD/AU

=> s e3
L17         138 "LOOFT C"/AU

=> e kalm e/au
E1            4     KALM C/AU
E2            2     KALM D/AU
E3          514 --> KALM E/AU
E4            1     KALM E A/AU
E5           69     KALM ERNST/AU
E6            3     KALM F/AU
E7           63     KALM H/AU
```

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E8            1      KALM H J/AU
E9            1      KALM HANS/AU
E10           3      KALM HELLE/AU
E11           1      KALM HENRY/AU
E12           1      KALM J K/AU

=> s e3
L18         514 "KALM E"/AU

=> e gellin j/au
E1            7      GELLIN GLORIA/AU
E2            7      GELLIN GLORIA L/AU
E3          456 --> GELLIN J/AU
E4            1      GELLIN J L/AU
E5            1      GELLIN J M/AU
E6            1      GELLIN JOEEL/AU
E7           43      GELLIN JOEL/AU
E8            5      GELLIN M/AU
E9           41      GELLIN M E/AU
E10           2      GELLIN R/AU
E11          12      GELLIN R G/AU
E12           2      GELLIN ROBERT G/AU

=> s e3
L19         456 "GELLIN J"/AU

=> e chardon p/au
E1           28      CHARDON NOBLAT S/AU
E2           36      CHARDON NOBLAT SYLVIE/AU
E3          460 --> CHARDON P/AU
E4            1      CHARDON P J/AU
E5           85      CHARDON PATRICK/AU
E6            2      CHARDON PAUL/AU
E7            1      CHARDON PENDARIES E/AU
E8            7      CHARDON R/AU
E9            1      CHARDON R E/AU
E10          10      CHARDON S/AU
E11           2      CHARDON S D/AU
E12           1      CHARDON SYLVIE/AU

=> s e3
L20         460 "CHARDON P"/AU

=> d his

     (FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006
L1          3955 S "AMPK"
L2          5373 S AMP (W) ACTIVATED (3W) KINASE?
L3          6016 S L1 OR L2
L4           155 S (MUSCULAR OR MUSCLE?)(W) L3
L5            66 S HUMAN AND L4
L6            30 DUP REM L5 (36 DUPLICATES REMOVED)
L7       2037417 S GAMMA
L8             6 S GAMMA AND L6
L9            23 S " R41Q" OR "V40I"
L10            0 S L6 AND L9
L11            1 S L3 AND L9
L12          154 S "PRKAG3"
L13           87 S L7 AND L12
L14            0 S L4 AND L13
L15           28 DUP REM L13 (59 DUPLICATES REMOVED)
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                E ANDERSEN L/AU
L16          523 S E3
                E LOOFT C/AU
L17          138 S E3
                E KALM E/AU
L18          514 S E3
                E GELLIN J/AU
L19          456 S E3
                E CHARDON P/AU
L20          460 S E3

=> s l15 or l16 or l17 or l18 or l19 or l20
L21         1957 L15 OR L16 OR L17 OR L18 OR L19 OR L20

=> s l21 and l4
L22            0 L21 AND L4

=> s l3 and l21
L23           26 L3 AND L21

=> dup rem l23
PROCESSING COMPLETED FOR L23
L24           21 DUP REM L23 (5 DUPLICATES REMOVED)

=> d 1-21 ibib ab

L24  ANSWER 1 OF 21  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
     reserved on STN
ACCESSION NUMBER:    2006033564  EMBASE
TITLE:               Characterization of the bovine PRKAG3 gene:
                     Structure, polymorphism, and alternative transcripts.
AUTHOR:              Roux M.; Nizou A.; Forestier L.; Ouali A.; Leveziel H.;
                     Amarger V.
CORPORATE SOURCE:    V. Amarger, Faculte des Sciences et Techniques, Unite de
                     Genetique Moleculaire Animale, Universite de Limoges, 123
                     av Albert Thomas, 87060 Limoges Cedex, France.
                     valerie.amarger@unilim.fr
SOURCE:              Mammalian Genome, (2006) Vol. 17, No. 1, pp. 83-92. .
                     Refs: 32
                     ISSN: 0938-8990  CODEN: MAMGEC
COUNTRY:             United States
DOCUMENT TYPE:       Journal; Article
FILE SEGMENT:        022     Human Genetics
LANGUAGE:            English
SUMMARY LANGUAGE:    English
ENTRY DATE:          Entered STN: 20060209
                     Last Updated on STN: 20060209
AB   The bovine PRKAG3 gene encodes the AMPK .gamma
     .3 subunit, one isoform of the regulatory .gamma. subunit of the
     AMP-activated protein kinase (AMPK).
     The AMPK plays a major role in the regulation of energy
     metabolism and mutations affecting the genes encoding the .gamma
     . subunits have been shown to influence AMPK activity.  The .
     gamma.3 subunit is involved in the regulation of AMPK
     activity in skeletal muscle and strongly inflences glycogen metabolism.
     Glycogen content in muscle is correlated to meat quality in livestock
     because it influences postmortem maturation process and ultimate pH.
     Naturally occurring mutations in the porcine PRKAG3 gene highly
     affect meat quality by influencing glycogen content before slaughter.  We
     present the characterization of the bovine PRKAG3 gene and a
     polymorphism analysis in three cattle breeds.  Thirty-two SNPs were
     identified among which 13 are in the coding region, one is in the 3' UTR,
     and 18 are in the introns.  Five of them change an amino acid in the
     PRKAG3 protein sequence.  Allelic frequencies were determined in
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the three breeds considered, and mutant alleles affecting the coding sequence are found at a very low frequency. Alternative splicing sites were identified at two positions of the gene, introducing heterogeneity in the population of proteins translated from the gene. .COPYRGT. Springer Science+Business Media, Inc. 2006.

L24 ANSWER 2 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2005625557 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16306365
TITLE: Changes in Exercise-Induced Gene Expression in 5'-**AMP-Activated** Protein **Kinase** {**gamma**}3-Null and {**gamma**}3 R225Q Transgenic Mice.
AUTHOR: Barnes Brian R; Long Yun Chau; Steiler Tatiana L; Leng Ying; Galuska Dana; Wojtaszewski Jorgen F P; Andersson Leif; Zierath Juleen R
CORPORATE SOURCE: Karolinska Institutet, Department of Surgical Sciences, Section of Integrative Physiology, von Eulers vag 4, 4th Floor, S-171 77 Stockholm, Sweden.. juleen.zierath@fyfa.ki.se
SOURCE: Diabetes, (2005 Dec) 54 (12) 3484-9. Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20051129
Last Updated on STN: 20051216

AB 5'-**AMP-activated** protein **kinase** (**AMPK**) is important for metabolic sensing. We used AMPKgamma3 mutant-overexpressing Tg-**Prkag3**(225Q) and AMPKgamma3-knockout **Prkag3**(-/-) mice to determine the role of the AMPKgamma3 isoform in exercise-induced metabolic and gene regulatory responses in skeletal muscle. Mice were studied after 2 h swimming or 2.5 h recovery. Exercise increased basal and insulin-stimulated glucose transport, with similar responses among genotypes. In Tg-**Prkag3**(225Q) mice, acetyl-CoA carboxylase (ACC) phosphorylation was increased and triglyceride content was reduced after exercise, suggesting that this mutation promotes greater reliance on lipid oxidation. In contrast, ACC phosphorylation and triglyceride content was similar between wild-type and **Prkag3**(-/-) mice. Expression of genes involved in lipid and glucose metabolism was altered by genetic modification of AMPKgamma3. Expression of lipoprotein lipase 1, carnitine palmitoyl transferase 1b, and 3-hydroxyacyl-CoA dehydrogenase was increased in Tg-**Prkag3**(225Q) mice, with opposing effects in **Prkag3**(-/-) mice after exercise. GLUT4, hexokinase II (HKII), and glycogen synthase mRNA expression was increased in Tg-**Prkag3**(225Q) mice after exercise. GLUT4 and HKII mRNA expression was increased in wild-type mice and blunted in **Prkag3**(-/-) mice after recovery. In conclusion, the **Prkag3**(225Q) mutation, rather than presence of a functional AMPKgamma3 isoform, directly promotes metabolic and gene regulatory responses along lipid oxidative pathways in skeletal muscle after endurance exercise.

L24 ANSWER 3 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2005604270 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16237515
TITLE: Role of **AMP-activated** protein **kinase** in the coordinated expression of genes controlling glucose and lipid metabolism in mouse white skeletal muscle.
AUTHOR: Long Y C; Barnes B R; Mahlapuu M; Steiler T L; Martinsson S; Leng Y; Wallberg-Henriksson H; Andersson L; Zierath J R

CORPORATE SOURCE: Department of Surgical Sciences, Section for Integrative Physiology, Karolinska Institute, Stockholm, Sweden.
SOURCE: Diabetologia, (2005 Nov) 48 (11) 2354-64. Electronic Publication: 2005-10-20.
Journal code: 0006777. ISSN: 0012-186X.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 20051115
Last Updated on STN: 20060127
Entered Medline: 20060126

AB AIMS/HYPOTHESIS: **AMP-activated** protein **kinase** (**AMPK**) regulates metabolic adaptations in skeletal muscle. The aim of this study was to investigate whether **AMPK** modulates the expression of skeletal muscle genes that have been implicated in lipid and glucose metabolism under fed or fasting conditions. METHODS: Two genetically modified animal models were used: **AMPK** gamma3 subunit knockout mice (**Prkag3**(-/-)) and skeletal muscle-specific transgenic mice (Tg-**Prkag3**(225Q)) that express a mutant (R225Q) gamma3 subunit. Levels of mRNA transcripts of genes involved in lipid and glucose metabolism in white gastrocnemius muscles of these mice (under fed or 16-h fasting conditions) were assessed by quantitative real-time PCR. RESULTS: Wild-type mice displayed a coordinated increase in the transcription of skeletal muscle genes encoding proteins involved in lipid/oxidative metabolism (lipoprotein lipase, fatty acid transporter, carnitine palmitoyl transferase-1 and citrate synthase) and glucose metabolism (glycogen synthase and lactate dehydrogenase) in response to fasting. In contrast, these fasting-induced responses were impaired in **Prkag3**(-/-) mice. The transcription of genes involved in lipid and oxidative metabolism was increased in the skeletal muscle of Tg-**Prkag3**(225Q) mice compared with that in wild-type mice. Moreover, the expression of the genes encoding hexokinase II and 6-phosphofrucktokinase was decreased in Tg-**Prkag3**(225Q) mice after fasting. CONCLUSIONS/INTERPRETATION: **AMPK** is involved in the coordinated transcription of genes critical for lipid and glucose metabolism in white glycolytic skeletal muscle.

L24 ANSWER 4 OF 21 EMBASE
ACCESSION NUMBER: 2005207470 EMBASE
TITLE: 5'-**AMP-activated** protein **kinase** regulates skeletal muscle glycogen content and ergogenics.
AUTHOR: Barnes B.R.; Glund S.; Long Y.C.; Hjalm G.; Andersson L.; Zierath J.R.
CORPORATE SOURCE: J.R. Zierath, Karolinska Institutet, Department of Surgical Sciences, Section of Integrative Physiology, von Eulers vag 4, S-171 77 Stockholm, Sweden. Juleen.Zierath@fyfa.ki.se
SOURCE: FASEB Journal, (2005) Vol. 19, No. 7, pp. 773-779. .
Refs: 31
ISSN: 0892-6638 CODEN: FAJOEC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050609
Last Updated on STN: 20050609

AB 5'-**AMP-activated** protein **kinase** (**AMPK**) activity is increased during exercise in an intensity- and glycogen-dependent manner. We previously reported that a mutation in the **AMPK.gamma**.S subunit (**Prkag3**(225Q)) increases **AMPK** activity and skeletal muscle glycogen content. Transfection

experiments revealed the R225Q mutation is associated with high basal **AMPK** activity and diminished AMP dependence. Thus, the R225Q mutation can be considered a loss-of-function mutation that abolished allosteric regulation by AMP/ATP, causing increased basal **AMPK** activity. We used **AMPK.gamma.S** transgenic (Tg-**Prkag3**(225Q)) and knockout (**Prkag3**(-/-)) mice to determine the relationship between **AMPK** activity, glycogen content, and ergogenics (ability to perform work) in isolated extensor digitorum longus skeletal muscle after contractions induced by electrical stimulation. Contraction-induced **AMPK** activity was inversely coupled to glycogen content in wild-type and Tg-**Prkag3**(225Q) mice, but not in **Prkag3**(-/-) mice, highlighting a partial feedback control of glycogen on contraction-induced **AMPK** activity in the presence of a functional **AMPK.gamma.S** isoform. Skeletal muscle glycogen content was positively correlated to work performance, regardless of genotype. Thus, chronic activation of **AMPK** by the **Prkag3**(225Q) mutation directly influences skeletal muscle ergogenics by enhancing glycogen content. In conclusion, functional studies of the **AMPK.gamma.S** isoform further support the close connection between glycogen content and exercise performance in skeletal muscle.

L24 ANSWER 5 OF 21 EMBASE

ACCESSION NUMBER: 2004416652 EMBASE

TITLE: The 5'-**AMP-activated** protein **kinase .gamma.**3 isoform has a key role in carbohydrate and lipid metabolism in glycolytic skeletal muscle.

AUTHOR: Barnes B.R.; Marklund S.; Steiler T.L.; Walter M.; Hjalm G.; Amarger V.; Mahlapuu M.; Leng Y.; Johansson C.; Galuska D.; Lindgren K.; Abrink M.; Stapleton D.; Zierath J.R.; Andersson L.

CORPORATE SOURCE: J.R. Zierath, Dept. of Surgical Sciences, Section for Integrative Physiology, Karolinska Institute, von Eulers vag 4, SE-171 77 Stockholm, Sweden. Juleen.Zierath@fyfa.ki.se

SOURCE: Journal of Biological Chemistry, (10 Sep 2004) Vol. 279, No. 37, pp. 38441-38447. .
Refs: 38
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041018
Last Updated on STN: 20041018

AB 5'-**AMP-activated** protein **kinase** (**AMPK**) is a metabolic stress sensor present in all eukaryotes. A dominant missense mutation (R225Q) in pig **PRKAG3**, encoding the muscle-specific **.gamma.**3 isoform, causes a marked increase in glycogen content. To determine the functional role of the **AMPK .gamma.**3 isoform, we generated transgenic mice with skeletal muscle-specific expression of wild type or mutant (225Q) mouse **.gamma.**3 as well as **Prkag3** knock-out mice. Glycogen resynthesis after exercise was impaired in **AMPK .gamma**.3 knock-out mice and markedly enhanced in transgenic mutant mice. An **AMPK** activator failed to increase skeletal muscle glucose uptake in **AMPK .gamma.**3 knock-out mice, whereas contraction effects were preserved. When placed on a high fat diet, transgenic mutant mice but not knock-out mice were protected against excessive triglyceride accumulation and insulin resistance in skeletal muscle. Transfection experiments reveal the R225Q mutation is associated with higher basal

AMPK activity and diminished AMP dependence. Our results validate the muscle-specific AMPK .gamma.3 isoform as a therapeutic target for prevention and treatment of insulin resistance.

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ACCESSION NUMBER: 2004335490 EMBASE
TITLE: UDP-glucose pyrophosphorylase is upregulated in carriers of the porcine RN(-) mutation in the AMP-activated protein kinase.
AUTHOR: Hedegaard J.; Horn P.; Lametsch R.; Moller H.S.; Roepstorff P.; Bendixen C.; Bendixen E.
CORPORATE SOURCE: Dr. E. Bendixen, Department of Food Sciences, Danish Inst. of Agric. Sciences, P.O. Box 50, DK-8830 Tjele, Denmark. Emoke.Bendixen@agrsci.dk
SOURCE: Proteomics, (2004) Vol. 4, No. 8, pp. 2448-2454. .
Refs: 40
ISSN: 1615-9853 CODEN: PROTC7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040819
Last Updated on STN: 20040819

AB The AMP-activated protein kinase (AMPK) plays a key role in the regulation of energy metabolism in eukaryotic cells acting as a metabolic sensor. In its activated form AMPK inhibits ATP consuming pathways and stimulates ATP generating pathways. A dominant mutation, denoted RN(-), in the porcine PRKAG3 gene, encoding the regulatory .gamma.3 subunit of AMPK, results in hyperaccumulation of glycogen in glycolytic skeletal muscle cells. To study the effects of this mutation on protein expression patterns in skeletal muscle, comparative proteome analysis of muscle samples from 12 animals (6 rn (+)/rn (+) and 6 RN(-)/rn (+)) was performed. The major finding of the proteome analysis was that the key enzyme in the synthesis of glycogen, UDP-glucose pyrophosphorylase, was significantly up-regulated in RN(-) carriers. This observation was subsequently supported by studies of enzyme activity and Northern blot analysis. Furthermore, the expression patterns of enzymes related to glycolysis and the citric acid cycle were also affected. Our data suggests that hyperaccumulation of glycogen mediated by the RN(-) mutation is due to an increased synthesis of glycogen.

L24 ANSWER 7 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1

ACCESSION NUMBER: 2004272200 EMBASE
TITLE: Assignment of two isoforms of the AMP-activated protein kinase γ subunits, PRKAG1 and PRKAG2 to porcine chromosomes 5 and 18, respectively by radiation hybrid panel mapping.
AUTHOR: Haberkern G.; Regenhard P.; Ottzen-Schirakow G.; Kalm E.; Looft C.
CORPORATE SOURCE: Dr. C. Looft, Tierzucht Tierhaltung Chrstn.-A., Olshausenstrasse 40, 24098 Kiel, Germany. clooft@tierzucht.uni-kiel.de
SOURCE: Cytogenetic and Genome Research, (2004) Vol. 106, No. 1, pp. 142A1-142A2. .
Refs: 7
ISSN: 1424-8581 CODEN: CGRYAJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
022 Human Genetics

029 Clinical Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 20040715
Last Updated on STN: 20040715

L24 ANSWER 8 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2004320557 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15222307
TITLE: Assignment of two isoforms of the **AMP-activated** protein **kinase** gamma subunits, PRKAG1 and PRKAG2 to porcine chromosomes 5 and 18, respectively by radiation hybrid panel mapping.
AUTHOR: Haberkern G; Regenhard P; Ottzen-Schirakow G; **Kalm E; Looft C**
CORPORATE SOURCE: Institute of Animal Breeding and Husbandry, Christian-Albrechts-University, Kiel, Germany.
SOURCE: Cytogenetic and genome research, (2004) 106 (1) 142. Journal code: 101142708. ISSN: 1424-859X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200412
ENTRY DATE: Entered STN: 20040630
Last Updated on STN: 20041219
Entered Medline: 20041203

L24 ANSWER 9 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2004133221 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15025572
TITLE: Determination of PRKAG1 coding sequence and mapping of PRKAG1 and PRKAG2 relatively to porcine back fat thickness QTL.
AUTHOR: Demeure O; Liaubet L; Riquet J; Milan D
CORPORATE SOURCE: Laboratoire de Genetique Cellulaire, INRA, BP 27, 31326 Castanet-Tolosan, France.
SOURCE: Animal genetics, (2004 Apr) 35 (2) 123-5. Journal code: 8605704. ISSN: 0268-9146.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040318
Last Updated on STN: 20040526
Entered Medline: 20040525
AB PRKAG1, PRKAG2 and **PRKAG3** encode three isoforms of **AMP-activated** protein **kinase gamma** chain. A major effect on meat quality and a medium effect on back fat thickness of the RN- mutation in the **PRKAG3** gene has previously been reported. We have now mapped PRKAG1 and PRKAG2 at expected locations on SSC5 and SSC18 by analysis of radiation hybrids (IMpRH panel). PRKAG2 has been mapped in a region where no quantitative trait loci (QTL) has been reported. PRKAG1 has been mapped close to (but probably outside) a region containing a QTL influencing fatness traits. We have determined the full coding sequence of PRKAG1. No missense mutation was identified when comparing the coding sequence of one Meishan and one Large White boars. Further work is, however, required to determine if a polymorphism in PRKAG1 could be responsible for a part of the variability observed on fatness traits.

L24 ANSWER 10 OF 21 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-24128 BIOTECHDS
TITLE: New transgenic non-human animals expressing an **AMP-**

activated protein kinase gamma 3
subunit, useful as models for improving treatment, prevention or diagnosis of diseases related to energy metabolism, e.g. obesity or type 2 diabetes;
involving vector-mediated gene transfer and expression in host cell for use in disease diagnosis and prevention

AUTHOR: ANDERSSON L; MARKLUND S
PATENT ASSIGNEE: AREXIS AB
PATENT INFO: WO 2003063586 7 Aug 2003
APPLICATION INFO: WO 2003-IB912 31 Jan 2003
PRIORITY INFO: US 2002-353430 1 Feb 2002; US 2002-353430 1 Feb 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-663404 [62]

AB DERWENT ABSTRACT:
NOVELTY - A transgenic non-human animal having integrated within its genome a transgene or a nucleic acid encoding an **AMP-activated** protein **kinasegamma3** subunit or its variant, where the nucleic acid is operably linked to a regulatory element, is new.

DETAILED DESCRIPTION - The transgene has a nucleotide sequence that hybridizes under stringent hybridization conditions with a nucleic acid having a nucleotide sequence complementary to a fully defined sequence of 1470 base pairs (N1) given in the specification, where the sequence encodes an **AMP-activated** protein **kinasegamma3** subunit or its variant, and where the transgene is operably linked to a promoter that drives expression in skeletal muscle. INDEPENDENT CLAIMS are included for the following: (1) an expression construct comprising a regulatory element operably linked to a nucleotide sequence having at least 75% sequence identity to the nucleotide sequence of N1, or a nucleotide sequence encoding a polypeptide having at least 75% sequence identity to a fully defined sequence of 489 amino acids (P1) given in the specification, or its portion, where the regulatory element is capable of mediating expression in skeletal muscle; (2) making a transgenic non-human animal cited above, comprising introducing the expression construct of (1) into an ovum, an embryo, or embryonic stem cells of a non-human animal; and (3) identifying a compound or composition for treating or preventing a disease related to energy metabolism, comprising: (a) administering a test compound or test composition to the transgenic non-human animal cited above, and evaluating the effect of the test compound or test composition on the energy metabolism of the transgenic non-human animal, where the test compound or test composition is identified as effective for the treatment or prevention of the disease related to energy metabolism if energy metabolism is altered; or (b) contacting a test compound or test composition with an organ, a tissue or cells derived from the transgenic non-human animal, and evaluating the effect of the test compound or test composition on the energy metabolism on the organ, tissue or cells, where the test compound or test composition is identified as effective for the treatment or prevention of the disease related to energy metabolism if energy metabolism is altered.

BIOTECHNOLOGY - Preferred Transgenic Animal: The transgenic non-human animal has an elevated glycogen content in skeletal muscle, and is selected from the group of mice, rats, rabbits, cats, dogs and pigs. The transgenic non-human animal is preferably a mouse or a pig. The transgene hybridizes under highly stringent conditions. The nucleic acid comprises a nucleotide sequence encoding a polypeptide having at least 75% sequence identity to the sequence of P1, a fully defined sequence of 489 amino acids (P2) given in the specification, or to a fragment of P1 or P2 at least 200 amino acids in length. The nucleic acid encodes a polypeptide having the amino acid sequence of P1 or P2, or an R225Q variant of the sequence of P1 or P2. The nucleic acid sequence comprises the nucleotide sequence of N1, a fully defined sequence of 1518 (N2) or 9100 (N3) base pairs given in the specification, a codon 225 variant of the sequence of N1 or N3, or a nucleotide sequence corresponding to the

mouse **Prkag3** gene. The regulatory element is a muscle specific regulatory element, such as a myosin light chain promoter, a myosin heavy chain promoter, a skeletal alpha actin promoter, a creatine kinase promoter, or an aldolase A promoter. Preferred Method: In making a transgenic non-human animal, the expression construct is microinjected into the ovum or embryo, or into embryonic stem cells, of the non-human animal. The expression construct is electroporated into the embryonic stem cells. In identifying a compound or composition for treating or preventing a disease related to energy metabolism, the tissue is skeletal muscle and the cells are muscle cells.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic. No biological data given.

MECHANISM OF ACTION - None given.

USE - The transgenic non-human animals are useful as models for improving treatment, prevention or diagnosis of diseases related to energy metabolism, or for identifying a compound or composition for treating or preventing a disease related to energy metabolism, e.g. obesity, dyslipidemia, insulin resistance syndrome, or type 2 diabetes. The expression constructs are useful for making transgenic non-human animals. (46 pages)

L24 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:610488 HCAPLUS
DOCUMENT NUMBER: 139:160792
TITLE: Human **AMP-activated kinase** (**AMPK**) .**gamma**.3 subunit gene **Prkag3** promoter and uses thereof
INVENTOR(S): Svensson, Thomas
PATENT ASSIGNEE(S): Arexis AB, Swed.
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003064465	A2	20030807	WO 2003-IB762	20030131
WO 2003064465	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2474005	AA	20030807	CA 2003-2474005	20030131
EP 1474520	A2	20041110	EP 2003-734809	20030131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005155091	A1	20050714	US 2003-503039	20030131
PRIORITY APPLN. INFO.:			US 2002-353429P P	20020201
			WO 2003-IB762 W	20030131

AB The invention provides an isolated promoter of human **Prkag3**, which encodes **AMP-activated kinase** (**AMPK**) subunit .**gamma**.3. **Prkag3** gene is muscle-specific and plays a key role in the regulation of energy metabolism in skeletal muscle. Specifically, various genetic motifs in **Prkag3** promoter for various transcription activators or repressors are identified. Expression constructs containing the **Prkag3** promoter

also are provided, as are methods of using such expression constructs to direct expression of a heterologous coding sequence. Host cells containing an expression construct of the invention are provided, as well as methods of using such cells to screen for compds. that transcriptionally modulate the activity of a **Prkag3** promoter.

L24 ANSWER 12 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:11621 BIOSIS
DOCUMENT NUMBER: PREV200400016870
TITLE: Mutation analysis of **AMP-activated** protein **kinase** subunits in inherited cardiomyopathies: Implications for kinase function and disease pathogenesis.
AUTHOR(S): Oliveira, Sandra Marisa J.; Ehtisham, Javed; Redwood, Charles S.; Ostman-Smith, Ingegerd; Blair, Edward M. [Reprint Author]; Watkins, Hugh
CORPORATE SOURCE: WTCHG, University of Oxford, Roosevelt Drive, Headington, Oxford, OX3 7BN, UK
eblair@molbiol.ox.ac.uk
SOURCE: Journal of Molecular and Cellular Cardiology, (October 2003) Vol. 35, No. 10, pp. 1251-1255. print.
ISSN: 0022-2828 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003

AB Familial hypertrophic cardiomyopathy (HCM) has been defined as a disease of the cardiac sarcomere, although sarcomeric protein mutations are not found in one third of cases. We have recently shown that HCM associated with Wolff-Parkinson-White syndrome (WPW) and conduction disease can be caused by mutations in PRKAG2, which encodes the gamma2 subunit of **AMPK**, an enzyme central to cellular energy homeostasis. **AMPK** is a heterotrimer composed of one catalytic subunit (alpha) and two regulatory subunits (beta and **gamma**). Seven known genes encode the subunit isoforms (alpha1, alpha2, beta1, beta2, gamma1, gamma2, gamma3) and all are expressed in the heart. To better understand the role of **AMPK** mutations in HCM/WPW and other inherited cardiomyophathies, all 7 subunit genes were screened for mutations in a panel of probands: 3 with HCM/WPW, 4 with DCM/WPW, 38 with HCM alone (in whom contractile protein mutations had not been found) and 13 with DCM alone. In total, 73 amplimers were screened in the 58 probands and a number of polymorphisms, including non-conservative substitutions, were identified. However, no further disease-causing mutations were found in any **AMPK** subunit gene. These results indicate that HCM with WPW is a distinct, but genetically heterogeneous, condition caused by mutations in PRKAG2 and in an unknown gene or genes, not involved in the **AMPK** complex. Mutations in PRKAG2 appear to specifically cause HCM with WPW and conduction disease, and not other inherited cardiomyopathies. As deleterious alleles were not found in other **AMPK** subunit isoforms, the mutations affecting PRKAG2 are likely to confer a specific alteration of **AMPK** function of particular importance in the myocardium.

L24 ANSWER 13 OF 21 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:1083412 SCISEARCH
THE GENUINE ARTICLE: 750PU
TITLE: The bovine 5 ' **AMPK** gene family: mapping and single nucleotide polymorphism detection
AUTHOR: McKay S D; White S N; Kata S R; Loan R; Womack J E (Reprint)
CORPORATE SOURCE: Texas A&M Univ, Dept Vet Pathobiol, College Stn, TX 77843 USA (Reprint)

COUNTRY OF AUTHOR: USA
SOURCE: MAMMALIAN GENOME, (DEC 2003) Vol. 14, No. 12, pp. 853-858. ISSN: 0938-8990.
PUBLISHER: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 25
ENTRY DATE: Entered STN: 21 Dec 2003
Last Updated on STN: 21 Dec 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The 5'-**AMP-activated** protein **kinase** (**AMPK**) family is an ancient stress response system whose primary function is regulation of cellular ATP. Activation of **AMPK**, which is instigated by environmental and nutritional stresses, initiates energy-conserving measures that protect the cell by inhibition and phosphorylation of key enzymes in energy-consuming biochemical pathways. The seven genes that comprise the bovine **AMPK** family were mapped in cattle by using a radiation hybrid panel. The seven genes mapped to six different cattle chromosomes, each with a LOD score greater than 10.0. PRKAA1 mapped to BTA 20, PRKAA2 and PRKAB2 to BTA 3, PRKAB1 to BTA 17, PRKAG1 to BTA 5, PRKAG2 to BTA 4, and **PRKAG3** to BTA 2. Five of the seven genes mapped to regions expected from human/cattle comparative maps. PRKAB2 and **PRKAG3**, however, have not been mapped in humans. We predict these genes to he located on HSA 1 and 2, respectively. Additionally, one synonymous and one non-synonymous single nucleotide polymorphism (SNP) were detected in **PRKAG3** in Bos taurus cattle. In an effort to determine ancestral origins, various herds of mixed breed cattle as well as other ruminant species were characterized for sequence variation in this region of **PRKAG3**. Owing to the physiological importance of this gene family, we believe that its individual genes are candidate genes for conferring resistance to diseases in cattle.

L24 ANSWER 14 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2003039119 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12546692
TITLE: Identification and characterization of **AMPK** **gamma** 3 mutations in the pig.
AUTHOR: Andersson L
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Box 597, S-751 24 Uppsala, Sweden.. Leif.Andersson@bmc.uu.se
SOURCE: Biochemical Society transactions, (2003 Feb) 31 (Pt 1) 232-5. Ref: 22
Journal code: 7506897. ISSN: 0300-5127.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030128
Last Updated on STN: 20031111
Entered Medline: 20031110

AB The RN(-) (rendement Napole, French for Napole yield) phenotype is common in Hampshire pigs and is characterized by a 70% increase in glycogen content in skeletal muscle and large effects on meat characteristics (pH, water content, technological yield and lean meat content). The phenotype is controlled by an autosomal dominant allele designated RN (-). The protein kinase AMP-activated **gamma** 3 subunit gene, **PRKAG3**, which encodes the **gamma** 3 isoform of **AMP** **-activated** protein **kinase** (**AMPK**), was identified as the causative gene for this phenotype by a pure positional

cloning approach. There are now several lines of evidence supporting our interpretation that the RN(-) phenotype is caused by a missense mutation (Arg(200)-->Gln) in **PRKAG3**. Recent data from another group have revealed the presence of a third functional allele at the **PRKAG3** locus, probably caused by a Val(199)-->Ile missense mutation. This allele has opposite effects compared with RN, as it is associated with a low glycogen content. We have confirmed the phenotypic effect of this third allele in a meat-quality study of a Hampshire/Landrace intercross. A physiological characterization of RN(-) carriers and normal pigs showed that the RN(-) pigs utilized glycogen during exercise to the same extent as normal pigs and they showed a significantly faster resynthesis of glycogen after exercise. The results strongly suggest that the Arg(200)-->Gln substitution is not associated with a defect in glycogen degradation, but rather with an increased glucose uptake in skeletal muscle.

L24 ANSWER 15 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2004080675 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14970705
TITLE: Molecular characterization and mutational screening of the **PRKAG3** gene in the horse.
AUTHOR: Park H B; Marklund S; Jeon J T; Mickelson J R; Valberg S J; Sandberg K; Andersson L
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden.
SOURCE: Cytogenetic and genome research, (2003) 102 (1-4) 211-6. Journal code: 101142708. ISSN: 1424-859X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040219
Last Updated on STN: 20040608
Entered Medline: 20040607

AB The **PRKAG3** gene encodes a muscle-specific isoform of the regulatory **gamma** subunit of **AMP-activated** protein **kinase** (**AMPK**). A major part of the coding **PRKAG3** sequence was isolated from horse muscle cDNA using reverse-transcriptase (RT)-PCR analysis. Horse-specific primers were used to amplify genomic fragments containing 12 exons. Comparative sequence analysis of horse, pig, mouse, human, Fugu, and zebrafish was performed to establish the exon/intron organization of horse **PRKAG3** and to study the homology among different isoforms of **AMPK gamma** genes in vertebrates. The results showed conclusively that the three different isoforms (gamma1, gamma2, and gamma3) were established already in bony fishes. Seven single nucleotide polymorphisms (SNPs), five causing amino acid substitutions, were identified in a screening across horse breeds with widely different phenotypes as regards muscle development and intended performance. The screening of a major part of the **PRKAG3** coding sequence in a small case/control material of horses affected with polysaccharide storage myopathy did not reveal any mutation that was exclusively associated with this muscle storage disease. The breed comparison revealed several potentially interesting SNPs. One of these (Pro258Leu) occurs at a residue that is highly conserved among **AMPK gamma** genes. In an SNP screening, the variant allele was only found in horse breeds that can be classified as heavy (Belgian) or moderately heavy (North Swedish Trotter, Fjord, and Swedish Warmblood) but not in light horse breeds selected for speed or racing performance (Standardbred, Thoroughbred, and Quarter horse) or in ponies (Icelandic horses and Shetland pony). The results will facilitate future studies of the possible functional significance of **PRKAG3** polymorphisms in horses.

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ACCESSION NUMBER: 2004103092 EMBASE
TITLE: Comparative sequence analysis of the **PRKAG3** region between human and pig: Evolution of repetitive sequences and potential new exons.
AUTHOR: Amarger V.; Erlandsson R.; Pielberg G.; Jeon J.-T.; Andersson L.
CORPORATE SOURCE: L. Andersson, Dept. Med. Biochem. and Microbiol., Uppsala University, Box 597, SE-751 24 Uppsala, Sweden. Leif.Andersson@imbim.uu.se
SOURCE: Cytogenetic and Genome Research, (2003) Vol. 102, No. 1-4, pp. 163-172. .
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ISSN: 1424-8581 CODEN: CGRYAJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040325
Last Updated on STN: 20040325

AB The **PRKAG3** gene encodes the .**gamma**.3 chain of AMPactivated protein kinase (**AMPK**). A non-conservative missense mutation in the **PRKAG3** gene causes a dominant phenotype involving abnormally high glycogen content in pig skeletal muscle. We have determined >126 kb (in 13 contigs) of porcine genomic sequence surrounding the **PRKAG3** gene and the corresponding mouse region covering the gene. A comparison of these **PRKAG3** sequences and the human sequence was conducted and used to predict evolutionarily conserved regions, including regulatory regions. A comparison of the human genomic sequence and a porcine BAC sequence containing the **PRKAG3** gene, revealed a conserved organization and the presence of three additional genes, CYP27A1 (cytochrome P450, family 27, subfamily A, polypeptide 1), STK36 (Serine Threonine Kinase 36), and the homolog of the unidentified human mRNA KIAA0173. Interspersed repetitive elements constituted 51.4 and 38.6% of this genomic region in human and pig, respectively. We were able to reliably align 12.6 kb of orthologous repeats shared between pig and human and these showed an average sequence identity of 72.4%. Our analysis revealed that the human KIAA0173 gene harbors alternative 5' untranslated exons originating from repetitive elements. This provides an obvious example how transposable elements may affect gene evolution. Copyright .COPYRGT. 2003 S. Karger AG, Basel.

L24 ANSWER 17 OF 21 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2002-13330 BIOTECHDS
TITLE: Screening animals to determine those likely to produce larger litters and improved meat quality traits involves assaying for the presence of polymorphisms in the **AMP** **activated** protein **kinase** regulatory **gamma** subunit gene;
DNA polymorphism identification on protein-kinase **PRKAG3** gene, DNA sequencing and BLAST comparison
AUTHOR: ROTHSCHILD M F; CIOBANU D C; MALEK M; PLASTOW G
PATENT ASSIGNEE: UNIV IOWA STATE RES FOUND INC
PATENT INFO: WO 2002020850 14 Mar 2002
APPLICATION INFO: WO 2000-US28283 8 Sep 2000
PRIORITY INFO: US 2001-299111 18 Jun 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-393850 [42]

AB DERWENT ABSTRACT:

NOVELTY - Screening (M1-3) animals to determine those more likely to (a) produce large litters, or (b) improved meat quality traits involves assaying for presence of a genotype in the sample of genetic material obtained from animal. The genotype is characterized by polymorphism(s) in the **AMP activated** protein **kinase** regulatory **gamma** subunit (**PRKAG3**) gene.

DETAILED DESCRIPTION - Screening (M1) animals to determine those most likely to produce larger litters involves obtaining a sample of genetic material from the animal, assaying for the presence of a genotype in the animal which is associated with the increased litter size,where the genotype is characterized by a polymorphism in the **PRKAG3** gene. Screening (M2) animals to determine those most likely to produce improved or favorable meat quality traits involves obtaining a biological sample of genetic material from the animal, assaying for the presence of a genotype in the animal which is associated with improved or favorable meat quality traits, where the genotype is characterized by a polymorphism (or a combination of at least two polymorphisms) in the **PRKAG3** gene (the polymorphism being one other than the ARG-ASN mutation at amino acid position 200). The polymorphism resulting in and characterized by an (a) amino acid of valine/isoleucine at position 199 and arginine at position 200, (b) an amino acid change of asparagine to threonine at amino acid position 30, or (c) an amino acid change of glycine to serine, or its equivalent as determined by BLAST comparison of a fully defined **PRKAG3** protein sequence of 464 amino acids (S2) as given in specification. Optionally, screening (M3) animals to determine those with a favorable combination of traits for meat quality and/or litter size, involves determining the alleles of **PRKAG3** gene present in an animal, the alleles comprising those which include one or more of the following: a polymorphic BsaHI, HpHI, or StyI site in the **PRKAG3** gene; determining the alleles of other markers for genes known to affect meat quality and/or litter size; and selecting for animals with favorable combinations of alleles and against those carrying unfavorable combinations. Also, screening animals to determine those more likely to have increased value for litter size and/or favorable meat quality traits involves obtaining a sample of genetic material from the animal; assaying the presence of a genotype in the animal which is associated with favorable litter size and/or meat quality, the genotype characterized by a combination of at least two polymorphisms in the **PRKAG3**, or by short interspersed element polymorphism in the **PRKAG3** gene. INDEPENDENT CLAIMS are also included for the following: (1) a nucleotide sequence comprising a fully defined sequence of 1873 nucleotides (I) which encodes upon expression a **PRKAG3** protein, further comprising a serine at position 52; (2) a nucleotide sequence (II) which encodes upon expression an **PRKAG3** protein comprising (a) an isoleucine or valine at position 199 and an arginine at position 200 or its equivalent of the protein, or (b) isoleucine at position 199, threonine at position 30, glycine at position 52 and arginine at position 200 or its equivalent of the protein; (3) a **PRKAG3** protein encoded by (I) or (II); and (4) identifying (M4) a genetic marker for meat quality and/or litter size in animals involves determining number of offspring produced by each female animal or the meat quality of the animal; determining the polymorphism in the **PRKAG3** or equivalent gene of each animal; the polymorphism as described above or their equivalents and associating the number of offspring produced by each female animal or meat quality with the polymorphism and thereby identifying a polymorphism for animal meat quality or litter size.

WIDER DISCLOSURE - Also disclosed is a method for assaying for protein conformational or sequence changes which occur in the presence of **PRKAG3** gene.

BIOTECHNOLOGY - Preferred Method: In (M1), the polymorphism results in an amino acid change from valine to isoleucine at amino acid number 199 of **PRKAG3** gene or its equivalent as determined by BLAST comparison of (S2); and is a transition of guanine to adenine at

nucleotide position 595 or its equivalent, or is a BsaHI polymorphism. Assaying the presence of genotype in the animal is carried out by restriction fragment length polymorphism analysis, minisequencing, matrix assisted laser desorption ionization-time-of-flight (MALDI-TOF), short interspersed nuclear element (SINE), heteroduplex analysis, single-strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis, or temperature gradient gel electrophoresis. (M1) further involves amplifying the amount of **PRKAG3** gene or its portion which contains the polymorphism. The amplification involves selecting forward and reverse sequence primers capable of amplifying a region of **PRKAG3** gene which contains a polymorphic BsaHI site. The forward and reverse primers are preferably selected from and based upon primer RNF and primer RNR. In (M2), the polymorphism resulting in and characterized by valine or isoleucine at position 199, is a transition of guanine to adenine at nucleotide position 595 or its equivalent. The assaying step involves a SINE polymorphism test, where the assay comprises amplifying the **PRKAG3** gene using primers from and based upon primer RP1F and primer PN52R2. The method further involves amplifying **PRKAG3** gene or its portion which contains the polymorphism, and includes the step of selecting primers RNF and RNR which are capable of amplifying region of **PRKAG3** gene which contains BsaHI site. The polymorphism resulting in and characterized by amino acid change of (a) Asn to Thr at amino acid position 30 of (S2), or (b) glycine to serine at amino acid position 52 of (S2) or its equivalent, is a transition of (i) adenine to cytosine at nucleotide position 89 of a fully defined **PRKAG3** gene sequence of 1873 nucleotides (S1) as given in specification or its equivalent as determined by a BLAST comparison, or StyI polymorphism; or (ii) guanine to adenine at nucleotide position 154 of (S1), or HpHI polymorphism, respectively. The genotype is assayed as described above. Assaying the presence of polymorphism of Asn to Thr at amino acid position 30 of (S2) or glycine to serine at position 52 of (S2), further includes amplifying **PRKAG3** gene or its portion which contains the polymorphism and includes selecting a forward and reverse primer e.g., primer RF1 and primer RN52R2, capable of amplifying a region of **PRKAG3** gene which contains a polymorphic StyI or HpHI site. In (M3), the determination of **PRKAG3** alleles involves determining the presence of at least one allele associated with at least one DNA marker (a microsatellite) linked either directly or indirectly to **PRKAG3** . (M4) further involves selecting animals for breeding which are predicted to have favorable meat quality or litter size by the marker. The analysis preferably involves digesting PCR amplified DNA with restriction enzyme such as BsaHI, HpHI or StyI. Preferred Nucleic Acid: (I) comprises a fully defined sequence of 1873 nucleotides, and encodes a **PRKAG3** protein having a sequence of 464 amino acids as given in specification.

USE - For screening animals e.g., pigs, to determine those most likely to exhibit improved meat quality traits, and to produce larger litters (claimed).

EXAMPLE - Several significant quantitative trait linkage (QTL) were detected on SSC15 (Malek et al., 2001) in the region where the **PRKAG3** gene was located between the markers SW1683 and SW1983. These included QTL for average glycogen content and glycolytic potential to be affected by the **PRKAG3** 200Q allele as well as the traits 24 hours ham and loin pH and 24 hours Hunter L values. The favorable allele at this QTL, which had an additive effect (the RN- mutation was dominant) was derived predominantly from the Berkshire breed. The **PRKAG3** gene was the unique candidate gene in this area, based on the recent development of the bacterial artificial chromosome (BAC) contig in the porcine RN region. First the founder animals, two Berkshire sires and nine Yorkshire dams were tested, for the published RN- substitution (R2000Q). All the founder animals had the rn+ allele (200R). By sequencing the entire coding region of the **PRKAG3** gene in BxY family founders and in four F3 individuals with extreme values for

meat quality, three missense mutations were identified. These were the T30N and the I199V substitutions previously described (Milan et al., 2000) and a new missense mutation (G52S). Another non-synonymous substitution (P53L) found by Milan et al., (2000) was not found to be segregating in the founders of the BxY family where they were all 53P. Due to the lack of information on the 5' untranslated region (UTR), rapid amplification of cDNA ends (RACE) was used in order to find the complete 5' flanking sequence and gene organization in that region. An intronic short interspersed nuclear element (SINE) polymorphism was discovered starting 79bp upstream of the start codon but this was present only in three Yorkshire grandams. Based on the differences in allele frequency of each site between the founders of the intercross family, the G52S and I199V substitutions were considered as the most likely candidates for the meat quality QTL reported previously. Using the I199V substitution the **PRKAG3** gene was mapped in the BxY linkage map to a position below the broad peak(s) of the QTL for glycogen, lactate ad glycolytic potential and 24 hour pH. After adding the **PRKAG3** I199V information the map length and marker order on SSC 15 was the same as in Milan et al., (2001). Using an association analysis significant effects were found of all three of the substitutions (T30N, G52S and I199V) on average glycogen and lactate content and also on glycolytic potential on the F2 BxY population. The most significant effects were revealed for I199V substitution for most of the traits analyzed, including glycogen and lactate content and glycolytic potential measures, but also in some of the meat quality traits associated with these measures. From the F2 data, the 30T, 52G and 199I alleles were favorable in terms of meat quality. The association study revealed that the largest effects across the lines and also within lines were obtained with the I199V substitution for all the traits analyzed. Significant effects, but smaller when compared to the I199V, were revealed for the T30n substitution in five of the traits when analyzed across lines. For the G52S substitution, significant effects were identified for only two of the traits (ham pH and loin Minolta L) in across lines analysis, and a different allele was identified as favorable for those traits. Also the **PRKAG3** alleles were also shown to have a significant association with litter size in animals. The polymorphism at codon 199 of **PRKAG3** was used to genotype sows with litter size data. Two lines were utilized, corresponding to a Landrace line (A) and a Duroc Synthetic line (B) that were previously found to have an association between this polymorphism and meat quality traits. A statistically significant association was found between the genotype and litter size traits (Total number born, number born alive) for line B in the First Parity. The heterozygote was found to have the largest litter size, in addition the 11 genotype had larger litters than the 22 homozygote suggesting an advantage for sows carrying at least one copy of allele. (109 pages)

L24 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:923085 HCAPLUS
DOCUMENT NUMBER: 138:249133
TITLE: A PCR-RFLP method to identify the RN- gene in retailed pork chops
AUTHOR(S): Meadus, W. J.; MacInnis, R.; Dugan, M. E. R.; Aalhus, J. L.
CORPORATE SOURCE: Lacombe Research Centre, Agriculture and Agri-Food Canada, Lacombe, AB, T4L 1W1, Can.
SOURCE: Canadian Journal of Animal Science (2002), 82(3), 449-451
CODEN: CNJNAT; ISSN: 0008-3984
PUBLISHER: Agricultural Institute of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The RN- phenotype in swine is associated with an increase in muscle glycogen. The increased glycogen leads to increased drip and cooking loss and inferior ham quality. RN- type pork was usually identified by a biochem.

measure of glycolytic potential (GP), which is an estimated sum of 2(glycogen, glucose, glucose-6-phosphate) + lactate. Recently, a mutation in the **PRKAG3** gene was reported to be the cause of the dominantly inherited RN- phenotype. This note describes a new BsrBI PCR-RFLP technique used to rapidly identify the **PRKAG3** mutation and its correlation with biochem. markers for RN- type pork. The **PRKAG3** BsrBI mutation was not found in 27% of retail pork chop samples that had high GP values.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 21 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2001-08298 BIOTECHDS
TITLE: New variant of the **gamma** subunit kinase for diagnosis or treatment of disorders associated with energy metabolism such as diabetes, obesity, and myopathy; for gene therapy and drug screening
AUTHOR: Andersson L; **Looft C**; **Kalm E**; Milan D; Robic A; Rogel-Gaillard C; Iannuccelli N; **Gellin J**; Le Roy P; **Chardon P**
PATENT ASSIGNEE: INRA; Andersson L; Looft C; Kalm E
LOCATION: Uppsala, Sweden; Bokelholm, Germany; Achterwehr, Germany; Paris, France.
PATENT INFO: WO 2001020003 22 Mar 2001
APPLICATION INFO: WO 2000-EP9896 11 Sep 2000
PRIORITY INFO: EP 2000-401388 18 May 2000; EP 1999-402236 10 Sep 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2001-244810 [25]
AB A **gamma** subunit (I) of a vertebrate adenosine monophosphate (**AMP**)-**activated kinase** (**AMPK**), in which (I) is a protein containing a sequence having at least 70% identity with a protein containing 305 amino acids fully defined is claimed. Also claimed are: a protein (II); a nucleic acid sequence (III); a nucleic acid sequence (IV); a nucleic acid fragment (V); a set of DNA primers (VI); a recombinant vector (VII); a host cell (VIII); a transgenic animal (IX); a knockout animal (X); a heterotrimeric **AMPK** (XI); detecting (M1) a metabolic disorder resulting from a mutation in a gene encoding (I); obtaining (M2) a pair of DNA primers; a pair of DNA primers (XII); and screening compounds able to modulate **AMPK** activity and energy metabolism in the absence of (I). A pair of DNA primers are useful for detecting a dysfunction of carbohydrate metabolism. A host cell, a transgenic animal or heterotrimeric **AMPK** are useful for screening compounds that modulate **AMPK** activity. A nucleic acid (III) is useful for detecting mutations in a **PRKAG3** (**gamma** subunit of **AMPK**) gene. (III) is useful as therapeutic for treating diabetes, obesity, cardiovascular diseases, etc. (71pp)

L24 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:763167 HCAPLUS
DOCUMENT NUMBER: 135:315318
TITLE: Variants of the human **AMP-activated** protein **kinase** .**gamma**.3 subunit and their use for diagnosis of a metabolic disease
INVENTOR(S): Andersson, Leif; Luthman, Holger; Marklund, Stefan
PATENT ASSIGNEE(S): Arexis AB, Swed.
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077305	A2	20011018	WO 2001-SE765	20010406
WO 2001077305	A3	20020228		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002142310	A1	20021003	US 2001-826581	20010405
US 2004121385	A1	20040624	US 2003-705137	20031110
PRIORITY APPLN. INFO.:			US 2000-195665P	P 20000407
			US 2001-826581	B1 20010405

AB This invention relates to new variants of the .**gamma**.3 subunit of human **AMP-activated** protein **kinase** (**PRKAG3**), to genes encoding the variants, and to their use. Nucleotide and encoded amino acid sequence of **PRKAG3** variants and methods of detecting such sequence variants are described. Methods for providing risk ests. for development of a metabolic disease also are described and are based on the presence or absence of **PRKAG3** sequence variants in a biol. sample.

L24 ANSWER 21 OF 21 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER:	2000280150 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 10818001
TITLE:	A mutation in **PRKAG3** associated with excess glycogen content in pig skeletal muscle.
AUTHOR:	Milan D; Jeon J T; **Looft** C; Amarger V; Robic A; Thelander M; Rogel-Gaillard C; Paul S; Iannuccelli N; Rask L; Ronne H; Lundstrom K; Reinsch N; **Gellin** J; **Kalm** E; Roy P L; **Chardon** P; Andersson L
CORPORATE SOURCE:	Laboratoire de Genetique Cellulaire, Institut National de la Recherche Agronomique (INRA), 31326 Castanet-Tolosan, France.
SOURCE:	Science, (2000 May 19) 288 (5469) 1248-51. Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200005
ENTRY DATE:	Entered STN: 20000606 Last Updated on STN: 20000606 Entered Medline: 20000525

AB A high proportion of purebred Hampshire pigs carries the dominant RN- mutation, which causes high glycogen content in skeletal muscle. The mutation has beneficial effects on meat content but detrimental effects on processing yield. Here, it is shown that the mutation is a nonconservative substitution (R200Q) in the **PRKAG3** gene, which encodes a muscle-specific isoform of the regulatory **gamma** subunit of adenosine monophosphate-activated protein kinase (**AMPK**). Loss-of-function mutations in the homologous gene in yeast (SNF4) cause defects in glucose metabolism, including glycogen storage. Further analysis of the **PRKAG3** signaling pathway may provide insights into muscle physiology as well as the pathogenesis of noninsulin-dependent diabetes mellitus in humans, a metabolic disorder associated with impaired glycogen synthesis.

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     (FILE 'HOME' ENTERED AT 13:57:31 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:57:53 ON 14 FEB 2006
L1          3955 S "AMPK"
L2          5373 S AMP (W) ACTIVATED (3W) KINASE?
L3          6016 S L1 OR L2
L4           155 S (MUSCULAR OR MUSCLE?)(W) L3
L5            66 S HUMAN AND L4
L6            30 DUP REM L5 (36 DUPLICATES REMOVED)
L7       2037417 S GAMMA
L8             6 S GAMMA AND L6
L9            23 S " R41Q" OR "V40I"
L10            0 S L6 AND L9
L11            1 S L3 AND L9
L12          154 S "PRKAG3"
L13           87 S L7 AND L12
L14            0 S L4 AND L13
L15           28 DUP REM L13 (59 DUPLICATES REMOVED)
                 E ANDERSEN L/AU
L16          523 S E3
                 E LOOFT C/AU
L17          138 S E3
                 E KALM E/AU
L18          514 S E3
                 E GELLIN J/AU
L19          456 S E3
                 E CHARDON P/AU
L20          460 S E3
L21         1957 S L15 OR L16 OR L17 OR L18 OR L19 OR L20
L22            0 S L21 AND L4
L23           26 S L3 AND L21
L24           21 DUP REM L23 (5 DUPLICATES REMOVED)
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	Issue Date	Pages	Document ID	Title
1	20060112	56	US 20060009410 A1	Effects of apolipoprotein B inhibition on gene expression profiles in animals
2	20060105	171	US 20060004052 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
3	20060105	447	US 20060003322 A1	Bioinformatically detectable group of novel regulatory genes and uses thereof
4	20051208	32	US 20050272082 A1	Alternatively spliced isoform of acetyl-CoA carboxylase 2 (ACC2)
5	20051208	96	US 20050272057 A1	Small segments of DNA determine animal identity and source
6	20051208	50	US 20050271666 A1	Regulation of human protein phosphatase IIc-like enzyme
7	20051201	15	US 20050267221 A1	Use of curcumin and analogues thereof as inhibitors of ACC2
8	20051201	23	US 20050266464 A1	C1q family member proteins with altered immunogenicity
9	20051110	11	US 20050250673 A1	Neurodegenerative disease treatment
10	20051103	23	US 20050245433 A1	Materials and methods for modulating metabolism
11	20051006	21	US 20050221354 A1	Nucleic acid arrays for monitoring expression profiles of drug target genes

	Issue Date	Pages	Document ID	Title
12	20050922	48	US 20050208551 A1	Novel PRKAG3 alleles and use of the same as genetic markers for reproductive and meat quality traits
13	20050915	26	US 20050202511 A1	AMP-activated protein kinase (AMPK) inhibitor screening assay
14	20050818	94	US 20050180949 A1	hC1Q/TNF7 and uses thereof
15	20050804	25	US 20050172348 A1	Transgenic animals expressing prkag3
16	20050804	58	US 20050171027 A1	Compositions for treating or preventing obesity and insulin resistance disorders
17	20050804	12	US 20050170349 A1	Variants of the alpha 1 subunit of human ampk
18	20050714	31	US 20050155091 A1	Prkag3 gene promoter and uses thereof
19	20050707	58	US 20050148643 A1	Carbamate compositions and methods fo rmodulating the activity of the CHK1 enzyme
20	20050407	176	US 20050075499 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
21	20050317	55	US 20050059153 A1	Electromagnetic activation of gene expression and cell growth
22	20050224	62	US 20050043381 A1	Aminopyrazole compounds

	Issue Date	Pages	Document ID	Title
23	20050224	9	US 20050042327 A1	Methods and compositions for increasing fermentation of a microorganism
24	20050217	86	US 20050038068 A1	Thienopyridones as AMPK activators for the treatment of diabetes and obesity
25	20050210	258	US 20050032166 A1	Polynucleotides encoding novel adiponectin receptor variants
26	20050106	27	US 20050002992 A1	Foods, beverages, condiments, spices and salad dressings with specialized supplements
27	20050106	21	US 20050002943 A1	Amp-kinase agonists or adenosine pro-drugs as immuno-stimulating agents
28	20041202	65	US 20040241802 A1	Adiponectin receptor and gene encoding the same
29	20041118	13	US 20040229805 A1	Agents for producing the health-benefits of repeated exercise
30	20041028	202	US 20040214255 A1	Compositions and methods for treating diabetes
31	20041014	20	US 20040204338 A1	Acetyl-coenzyme a carboxylase 2 as a target in the regulation of fat burning, fat accumulation, energy homeostasis and insulin action
32	20041007	18	US 20040197265 A1	Methods and pharmaceuticals for treating muscle insulin resistance and related conditions

	Issue Date	Pages	Document ID	Title
33	20040902	23	US 20040170705 A1	Compositions and methods for non-insulin glucose uptake
34	20040812	76	US 20040156826 A1	Treatment of patients with multiple sclerosis based on gene expression changes in central nervous system tissues
35	20040708	99	US 20040132025 A1	Ampk-related serine/threonine kinase, designated snark
36	20040624	21	US 20040121385 A1	Variants of the human AMP-activated protein kinase gamma 3 subunit
37	20040617	14	US 20040115708 A1	Method of screening agents for the treatment and prevention of cancer and cachexia and the new use of specific agents for the treatment and prevention of cancer and cachexia
38	20040304	21	US 20040043013 A1	Metabolic uncoupling therapy
39	20040226	259	US 20040038207 A1	Gene expression in bladder tumors
40	20040219	311	US 20040033506 A1	Polynucleotides encoding novel human mitochondrial and microsomal glycerol-3-phosphate acyl-transferases and variants thereof
41	20040129	84	US 20040018522 A1	Identification of dysregulated genes in patients with multiple sclerosis

	Issue Date	Pages	Document ID	Title
42	20031113	28	US 20030212034 A1	Method of treatment of obesity and paralyzed muscle and ergogenic aids
43	20031113	44	US 20030212014 A1	Methods fo treating conditions associated with insulin resistance with aicar, (5-amino-4-imidazole carboxamide riboside) and related compounds
44	20031113	13	US 20030212013 A1	Use of amp kinase activators for treatment type 2 diabetes and insulin resistance
45	20030206	20	US 20030028912 A1	ACC2-knockout mice and uses thereof
46	20030123	49	US 20030017470 A1	Novel PRKAG3 alleles and use of the same as genetic markers for reproductive and meat quality traits
47	20021003	13	US 20020142310 A1	Variants of the human AMP-activated protein kinase gamma 3 subunit
48	20020815	17	US 20020112253 A1	Acetyl-coenzyme a carboxylase 2 as a target in the regulation of fat burning, fat accumulation, energy homeostasis and insulin action
49	20020801	17	US 20020104111 A1	ACC2-Knockout mice and uses thereof

	Issue Date	Pages	Document ID	Title
50	20051122	163	US 6967198 B2	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
51	20050830	247	US 6936417 B2	Gene expression in bladder tumors
52	20050719	46	US 6919177 B2	PRKAG3 alleles and use of the same as genetic markers for reproductive and meat quality traits
53	20050111	10	US 6841348 B1	Methods for identifying and using maintenance genes
54	20040622	66	US 6753314 B1	Protein-protein complexes and methods of using same
55	20040511	18	US 6734337 B2	Acetyl-coenzyme A carboxylase 2 as a target in the regulation of fat burning, fat accumulation, energy homeostasis and insulin action
56	20030415	21	US 6548738 B2	ACC2-knockout mice and uses thereof
57	20030128	80	US 6511800 B1	Methods of treating nitric oxide and cytokine mediated disorders
58	20021231	65	US 6500938 B1	Composition for the detection of signaling pathway gene expression
59	20020101	227	US 6335170 B1	Gene expression in bladder tumors
60	20010710	46	US 6258547 B1	Nucleic acid encoding amp-activated protein kinase

	Issue Date	Pages	Document ID	Title
61	20000926	30	US 6124125 A	AMP activated protein kinase
62	19981208	95	US 5846720 A	Methods of determining chemicals that modulate expression of genes associated with cardiovascular disease
63	19961203	93	US 5580722 A	Methods of determining chemicals that modulate transcriptionally expression of genes associated with cardiovascular disease

	Issue Date	Pages	Document ID	Title
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2	20030123	49	US 20030017470 A1	Novel PRKAG3 alleles and use of the same as genetic markers for reproductive and meat quality traits
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1	20060105	447	US 20060003322 A1	Bioinformatically detectable group of novel regulatory genes and uses thereof
2	20051117	307	US 20050255458 A1	Drug discovery assays based on the biology of chronic disease
3	20050922	48	US 20050208551 A1	Novel PRKAG3 alleles and use of the same as genetic markers for reproductive and meat quality traits
4	20050113	179	US 20050009771 A1	Methods and systems for identifying naturally occurring antisense transcripts and methods, kits and arrays utilizing same
5	20050106	212	US 20050003341 A1	Drug discovery assays based on the biology of atherosclerosis, cancer, and alopecia
6	20041028	70	US 20040214792 A1	Methods of treating inflammation
7	20040205	73	US 20040023207 A1	Assays for drug discovery based on microcompetition with a foreign polynucleotide
8	20040205	72	US 20040023206 A1	Methods for chronic disease diagnosis based on microcompetition with a foreign polynucleotide
9	20030501	78	US 20030082511 A1	Identification of modulatory molecules using inducible promoters
10	20030410	173	US 20030069199 A1	Treatment methods based on microcompetition for a limiting GABP complex
11	20030410	172	US 20030068616 A1	Drug discovery assays based on microcompetition for a limiting GABP complex

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14	20011016	6	US 6304143 B1	Amplifier slew rate boosting scheme
15	19981208	95	US 5846720 A	Methods of determining chemicals that modulate expression of genes associated with cardiovascular disease
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